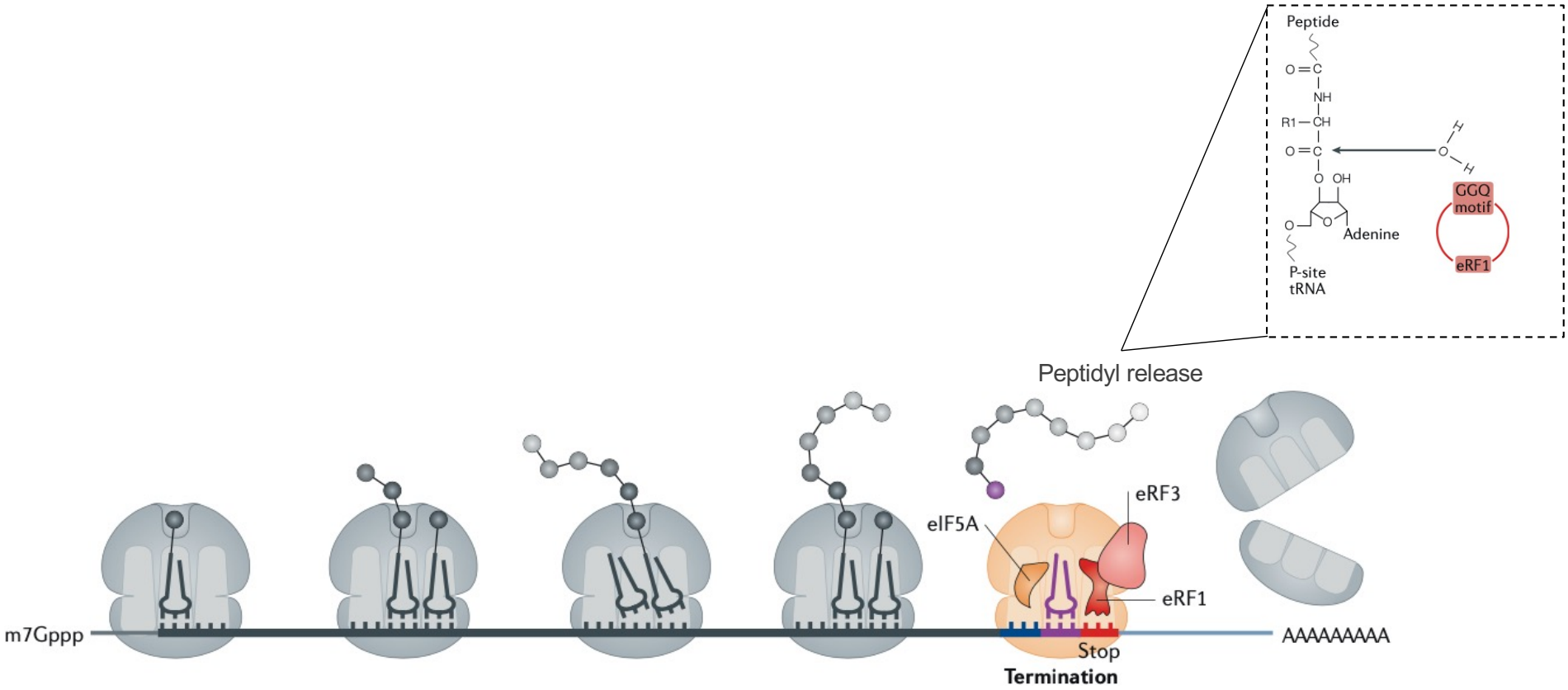
Quality controls in translation

Translation termination

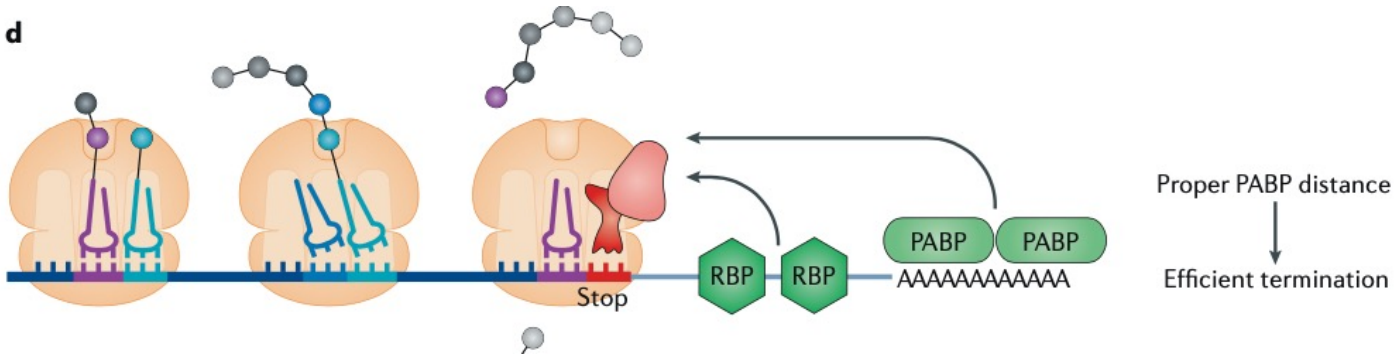
When the ribosome encounters a termination (stop) codon, eukaryotic peptide chain **release factor 1** (**eRF1**) is delivered by **eRF3** to catalyse peptidyl hydrolysis at the ribosome peptidyl-transferase centre. eIF5A binds in the ribosomal E site to stimulate eRF1-mediated hydrolysis.



RNA- binding proteins regulate translation termination

- The stop codon context could also affect the termination process by recruiting RNA-binding proteins that interact with release factors or with the ribosome. Recent work on poly(A)binding protein (PABP) has suggested that it may influence the efficiency of termination.

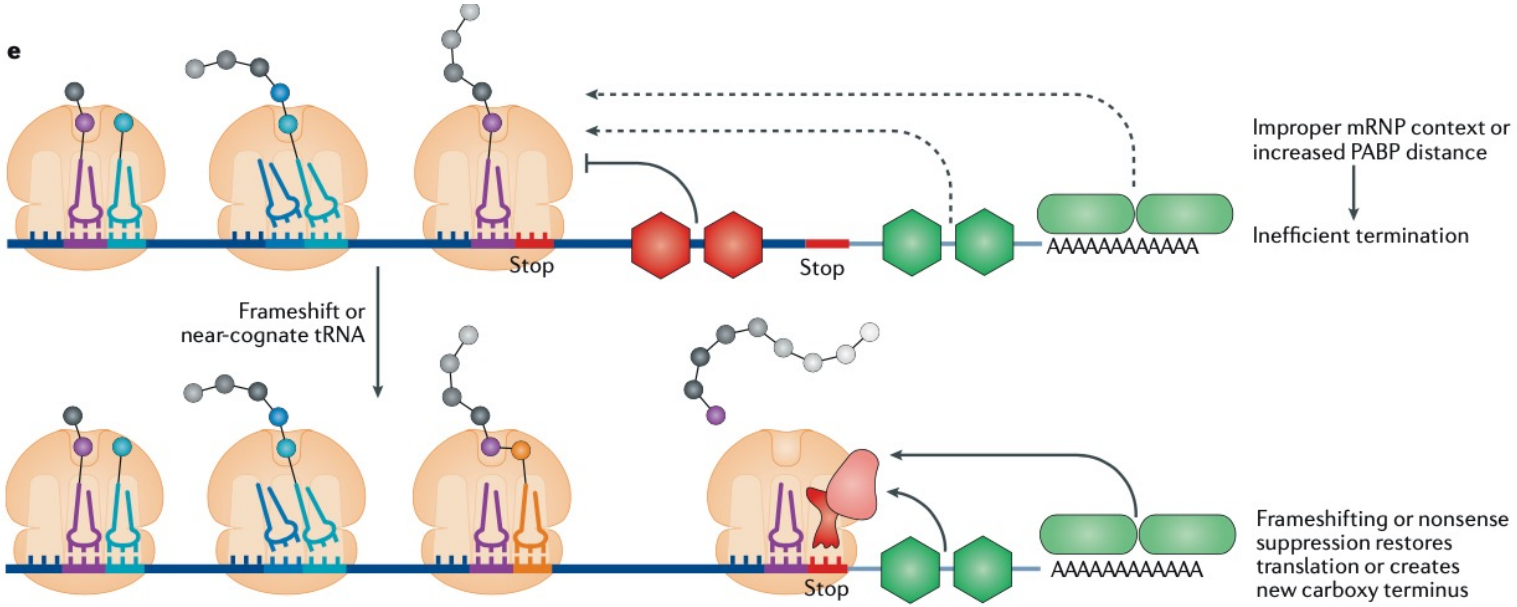
- PABP can directly promote the recruitment of eRF1–eRF3 to a terminating ribosome. Subsequent biochemical experiments also revealed that PABP stimulated the peptidyl-hydrolysis activity of eRF1–eRF3, although the mechanism is still unknown.



RNA- binding proteins regulate translation termination

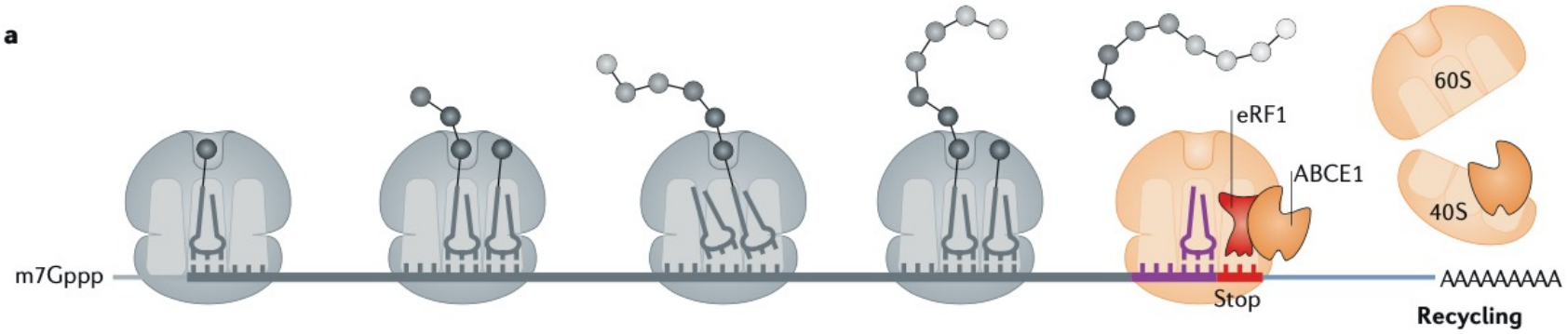
- Some ciliates and trypanosomes can use the three canonical stop codons to encode amino acids (sense) at some sites. Stop codons are recognized by aminoacylt-RNA as substrates by default unless they are located sufficiently close to the poly(A) tail (thus PABP), in which case they are recognized by the canonical eRFs.

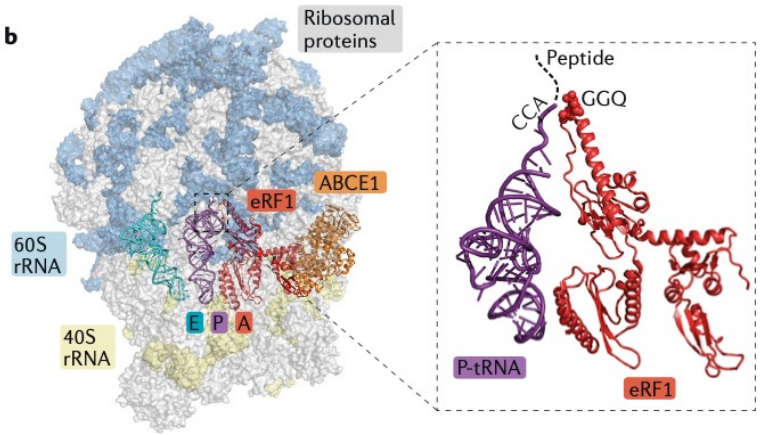
- Another example is heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1, which promotes readthrough of the vascular endothelial growth factor A mRNA to create an isoform with a unique carboxy terminus.



Ribosome recycling

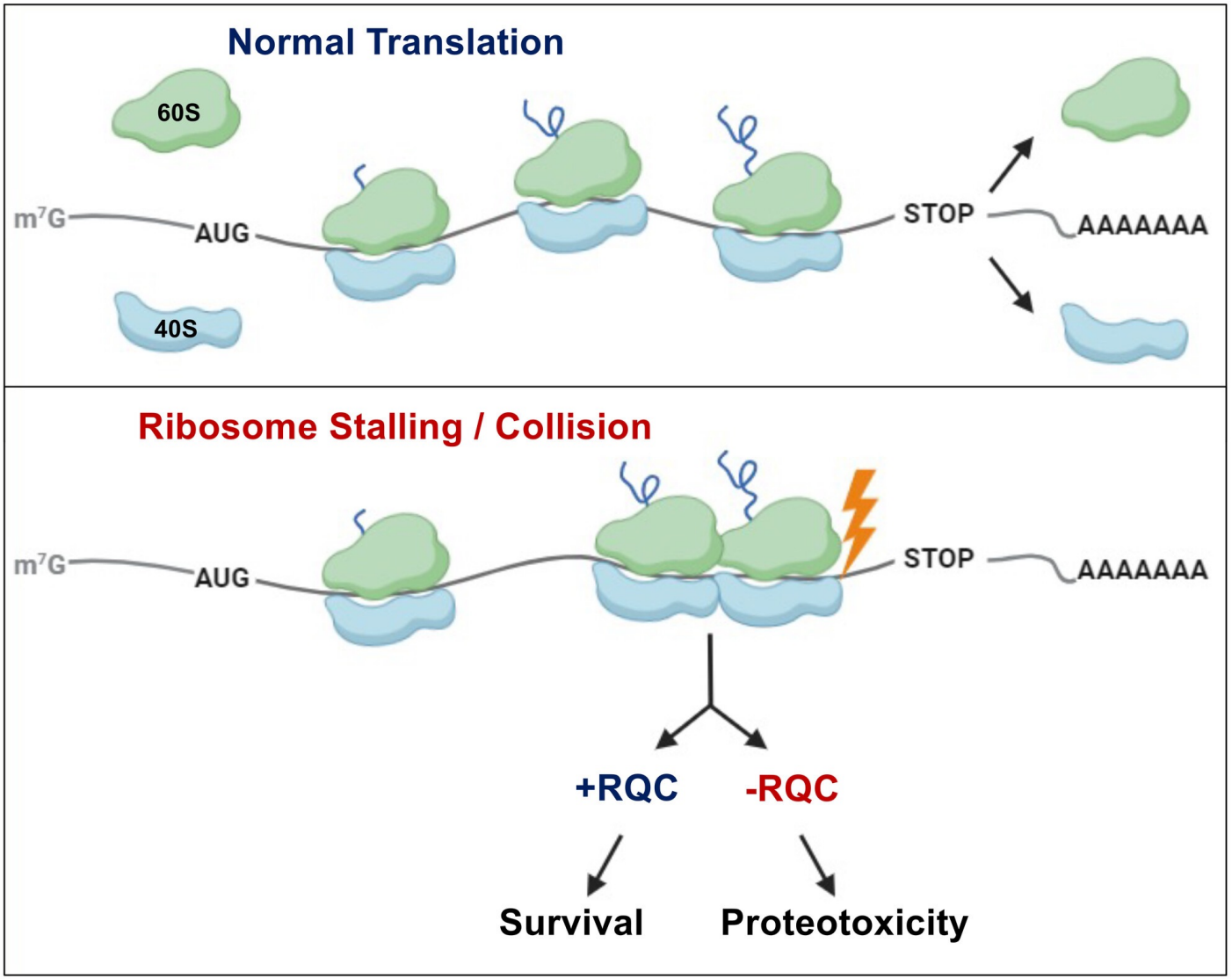
ATP-binding cassette subfamily E member 1 (ABCE1) binds to 80S ribosomes loaded with eRF1 and uses the power generated from ATP binding and hydrolysis to dissociate the ribosomal subunits. ABCE1 remains bound to the 40S subunit to stimulate subsequent translation initiation steps





Following subunit dissociation, the mRNAs and tRNAs must also be removed from the 40S subunit, potentially through the activity of ligatin (also known as eIF2D) or the related protein complex malignant T cell amplified sequence 1 (MCTS1)–density regulated protein (DENR)

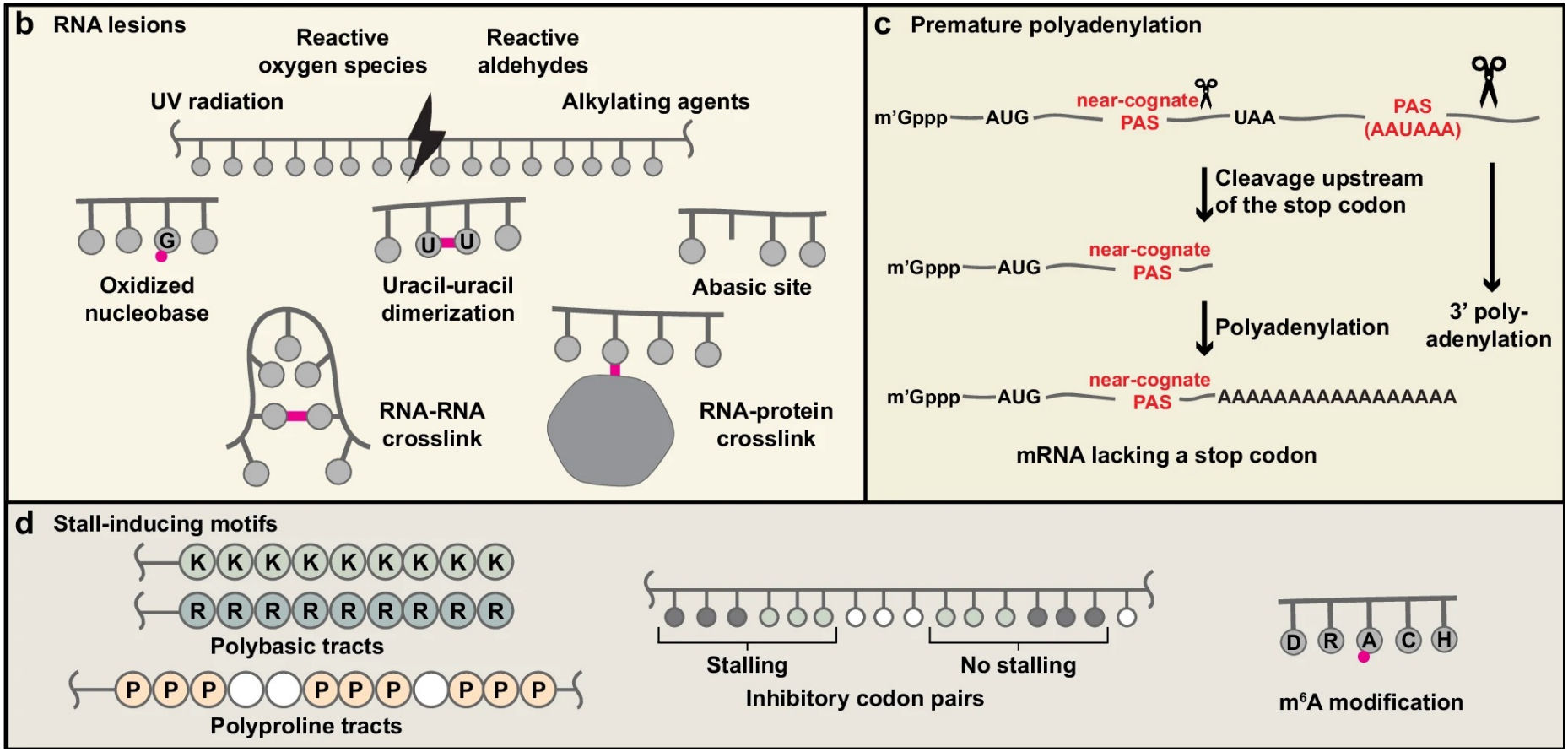
Stalled ribosomes collide with trailing ribosomes



RQC: Ribosome-associated quality control

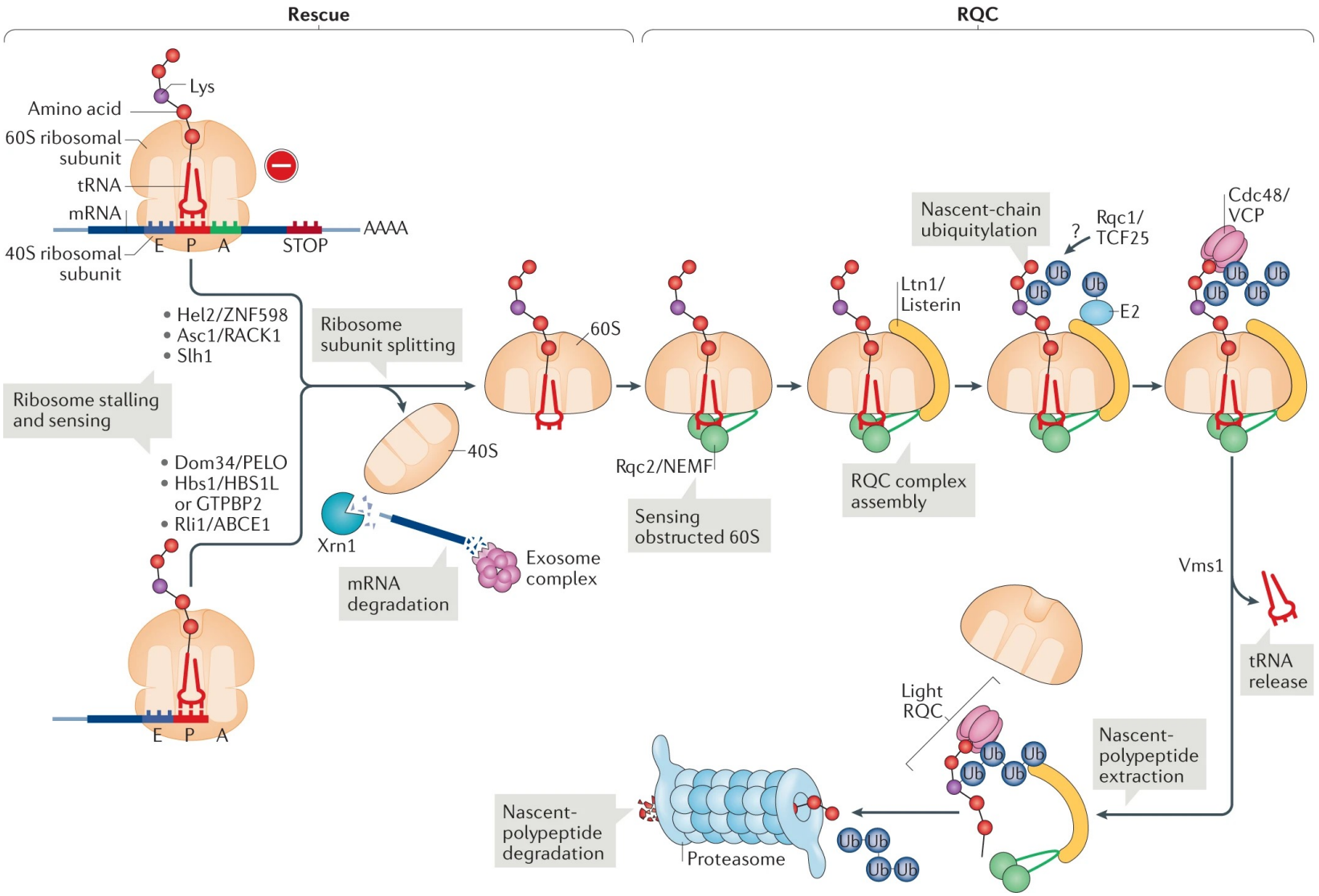
Causes of ribosome stalling

Stalling is caused by: b) **mRNA damage**, c) **premature polyadenylation**, 3) **specific codons**, **RNA modifications** or **nascent peptide features**.



Chang and Choe, 2026. *Exp Mol Med*

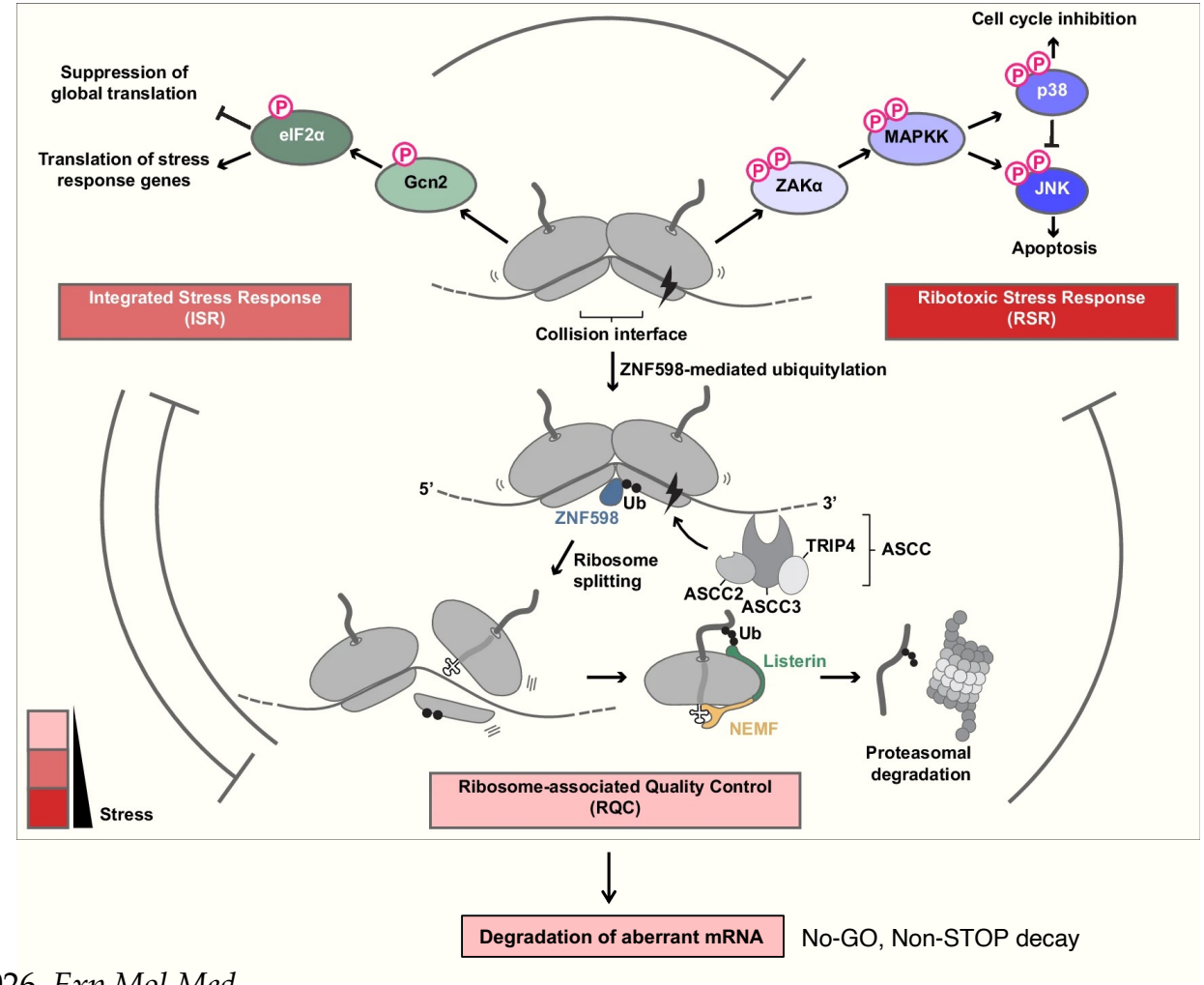
Translational quality control



Vms1 is a paralogue of the eukaryotic translation termination factor eRF1, a peptidyl-tRNA hydrolase that releases nascent chains in canonical translation termination

Collided ribosomes activate specific response pathways

When ribosomes stall and collide, cells activate downstream pathways with two main functions: (1) resolving stalled ribosomes by splitting and recycling subunits; and (2) preventing additional stalling events. If stalling persists, cells further engage broader stress responses, including the integrated stress response (ISR) and the ribotoxic stress response (RSR).



Chang and Choe, 2026. *Exp Mol Med*

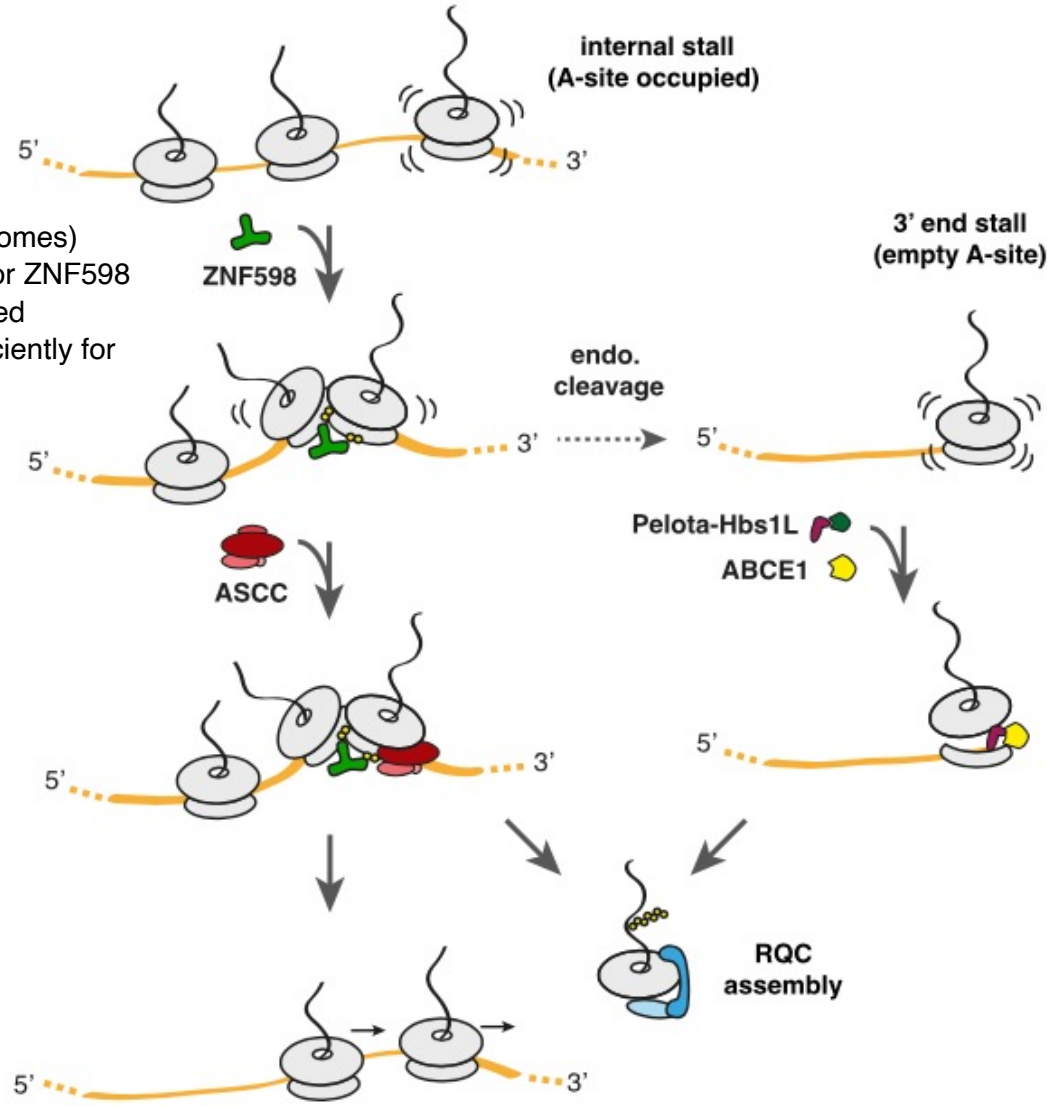
Conserved quality-control factors for aberrant translation in eukaryotes

Quality controls		Functions		Yeast	Mammals
RQC	Aberrant ribosome recognition	Collision sensor		Hel2	ZNF598
		RQT complex	RNA helicase	Slh1	ASCC3
			K63-linked polyUb binding	Cue3 Rqt4	ASCC2 hRQT4
	Aberrant product degradation	E3 ubiquitin ligase Ubiquitination factor AAA$^+$ ATPase factor Cdc48 cofactor CAT-tailing factor Peptide-releasing factor		Ltn1 Rqc1 Cdc48 Ufd1, Npl4 Rqc2 Vms1	LTN1/Listerin TCF25 p97/VCP UFD1, NPL4 NEMF ANKZF1
18S NRD		Slow ribosome sensor Stalled ribosome sensor		Mag2 Fap1	RNF10 ? (NFX1)
NGD		Stalled ribosome sensor Ribosome dissociation		Dom34 Rli1	PELO ABCE1

This summarizes the major components of the RQC and NGD pathways and lists their homologous factors in yeast and mammals. Factors are grouped by their functional roles, including collision sensing, polyubiquitin recognition, ribosome dissociation, CAT tailing, ubiquitination, peptide release and downstream degradation. The table highlights conserved modules, such as the Hel2/ZNF598 collision-sensing axis, the RQT complex, ubiquitin E3 ligases (LTN1/Listerin), AAA+ ATPases (Cdc48/p97), CAT-tailing factors (Rqc2/NEMF) and peptidyl-tRNA hydrolysis factors (Vms1/ANKZF1), illustrating the evolutionary conservation of aberrant ribosome recognition and nascent-chain quality-control mechanisms.

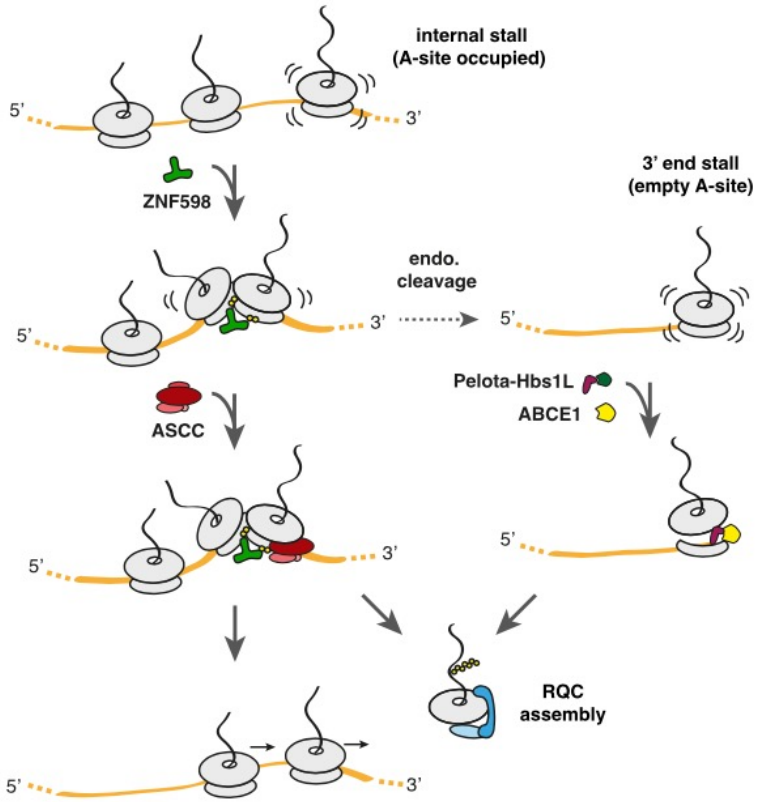
Ribosome rescue

While disomes (two collided ribosomes) represent the minimal substrate for ZNF598 recognition, trisomes (three collided ribosomes) are targeted more ef ciently for ubiquitylation



The ASC-1 Complex (ASCC) Disassembles Collided Ribosomes

Ribosomes that stall internally within an mRNA are recognized and resolved by a different mechanism than ribosomes that stall close to the 3′-end of an mRNA (Pelota/Hbs1). With an internal stall, ribosome collision recruits the ubiquitin ligase **ZNF598 (Hel2)** to ubiquitinate 40S proteins. Ubiquitylated 40S ribosomal proteins recruit the ribosome-splitting machinery **ASC-1 complex (ASCC)** in mammals. **ASCC** then acts on the lead ribosome to liberate a 60S-peptidyl-tRNA species that is targeted by **ribosome-associated quality control** (**RQC**). The trailing ribosomes can then continue elongation. Without ASCC, collided ribosomes are subject to endonucleolytic cleavage between ribosomes to generate ribosome-nascent chain complexes that are now stalled at or close to the 3′ end of the mRNA (right). Such species are dissociated by Pelota-Hbs1L-ABCE1 to generate 60S-peptidyl-tRNA complexes that are engaged by RQC.

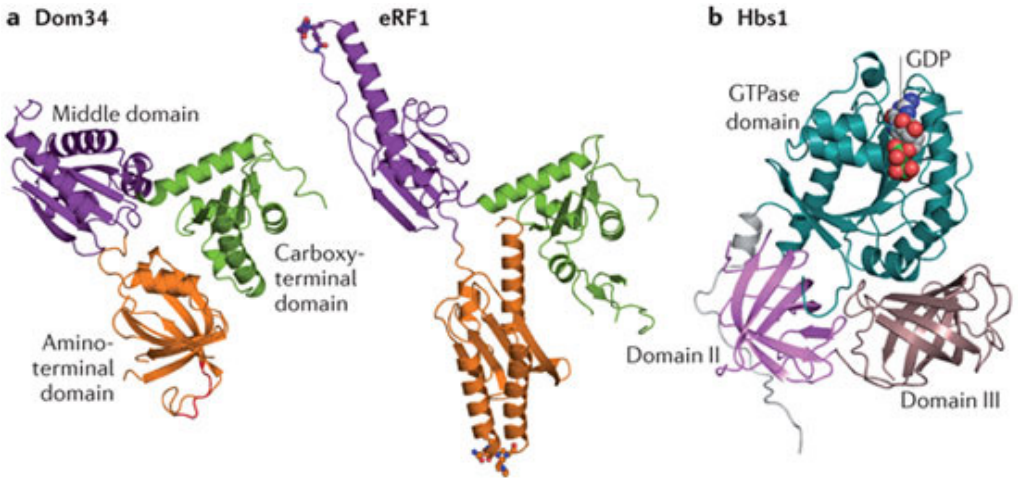


Juszkiewicz et al., 2020. Mol Cell

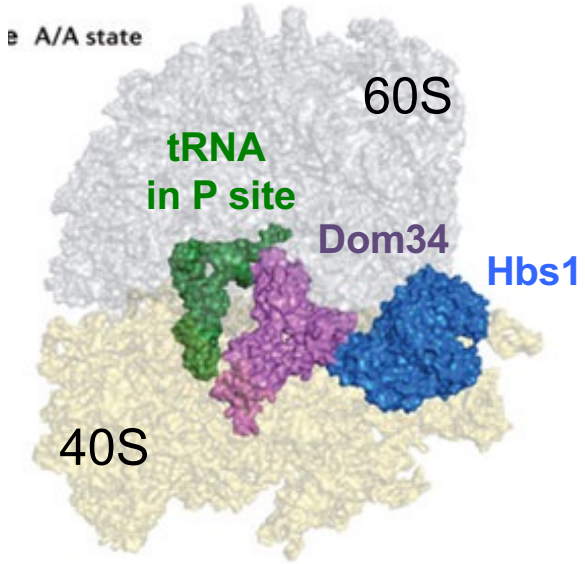
Ribosome rescue

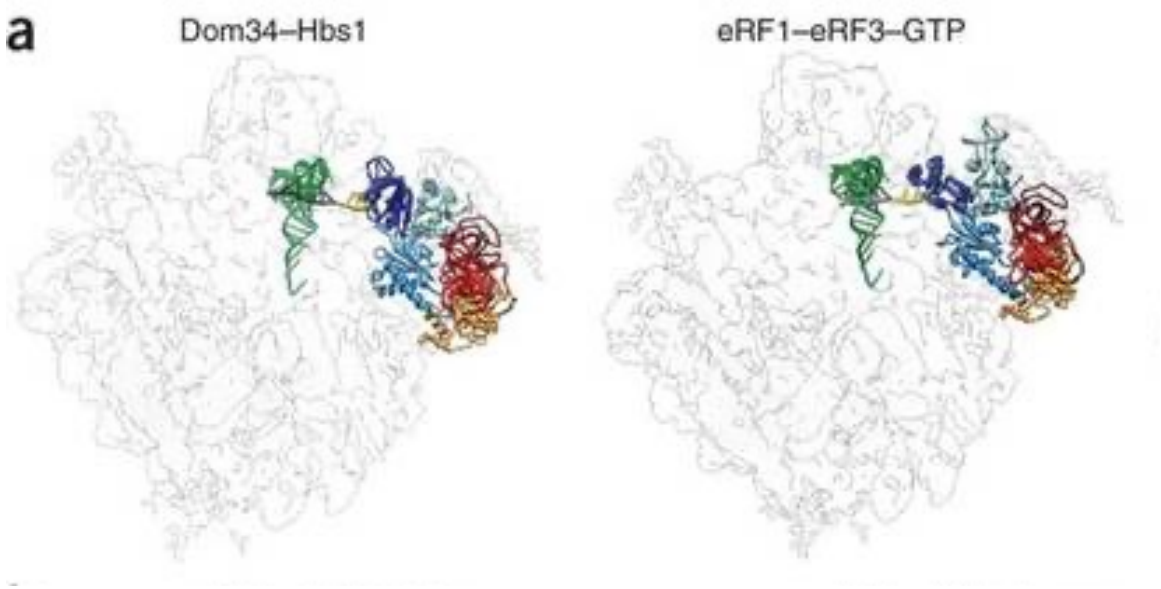
Dom34 in yeast (also known as Pelota or PELO in metazoans) is delivered by the GTPase **Hbs1** (an eRF3 homolog) to the empty A-site of ribosomes stalled at the 3′ end of truncated mRNA.

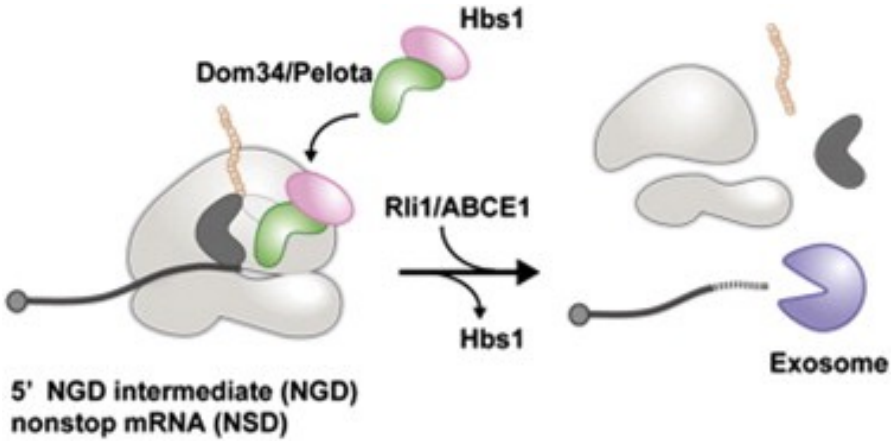
Dom34 is structurally similar to eRF1. However, it does not contain domain that recognizes stop codons and it does not contain the GGQ motif that catalyses peptidyl hydrolysis, leaving the peptidyl-tRNA attached to the large ribosomal subunit. Dom34 is delivered to the ribosome by Hbs1 (an eRF3 homolog).



Dom34-Hbs1 Play a general role in the dissociation of stalled ribosomes







As in canonical termination, the ATPase ABCE1/Rli1 mediates ribosome splitting.

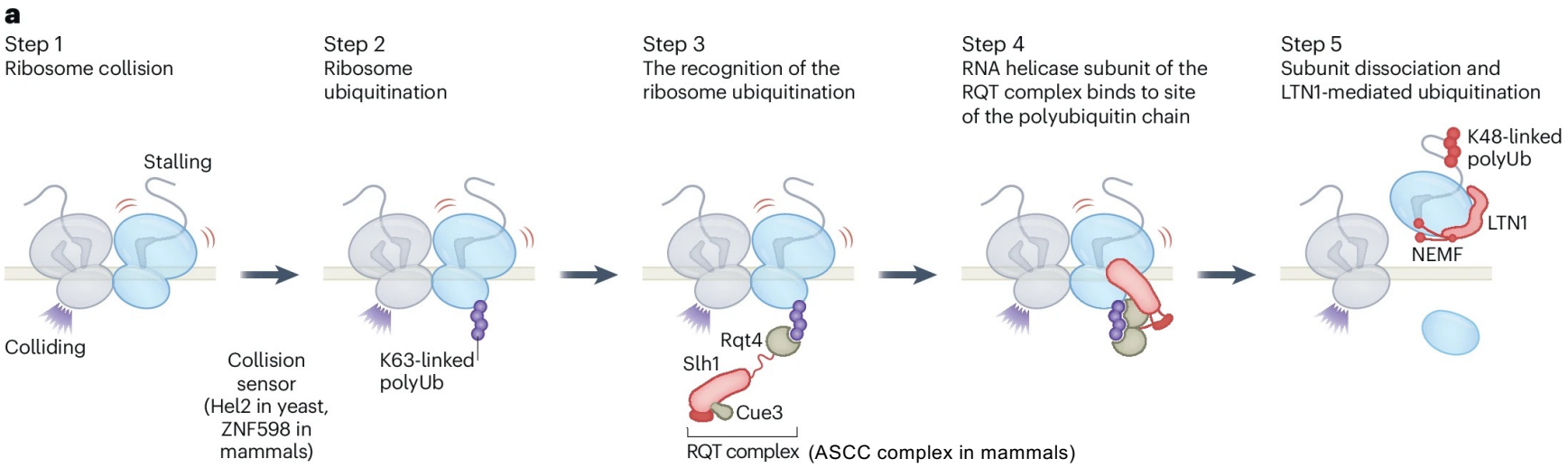
Ribosome-associated Quality Control (RQC)

If a ribosome will never successfully reach the correct termination codon, the protein product is necessarily truncated and is very likely to be defective; even if this truncated polypeptide could fold into a stable protein, it might lack key downstream domains and hence be functionally impaired or have dominant-negative effects. Thus, it would be advantageous for the cell to degrade these incomplete nascent chains by using the criteria of truncation rather than their capacity to fold.

Thus, **ribosome-associated quality control (RQC)** eliminates the partially synthesized protein products from ribosomes that stall before reaching the stop codon.

RQC senses and resolves collided ribosomes

Ribosome collisions trigger LTN1-mediated proteasomal degradation via subunit dissociation. **Step 1**. Ribosome collision: translation stalls on a poly(A) tail of a nonstop mRNA, a poly(A) tract within an open reading frame, runs of nonoptimal codons, a stall-inducing nascent polypeptide in the exit tunnel or on mRNA modification and/or damage, causing trailing ribosomes to collide with a stalled leading ribosome. **Step 2**. Ribosome ubiquitination: the collision sensor recognizes disome or trisome architectures and predominantly assembles K63-linked polyubiquitin chains on uS10. **Step 3.** Recognition of ribosome ubiquitination by the **RQT (ASCC) complex**: Cue3 (ASCC2 in mammals) and Rqt4 (hRQT4 in mammals) bind ubiquitin K63 chains on uS10. **Step 4**. The RNA helicase subunit of RQC complex **Slh1** (**ASCC3** in mammals) binds K63-linked polyubiquitin chains on uS10 destabilizing 40S. **Step 5.** Subunit dissociation and **LTN1**-mediated ubiquitination: the RQT complex pulls on the mRNA via the RNA helicase **Slh1** (**ASCC3** in mammals) to split collided ribosomes into the 40S and 60S subunits. **LTN1** then binds the 60S and ubiquitinates the aberrant nascent chain attached to peptidyl-tRNA.

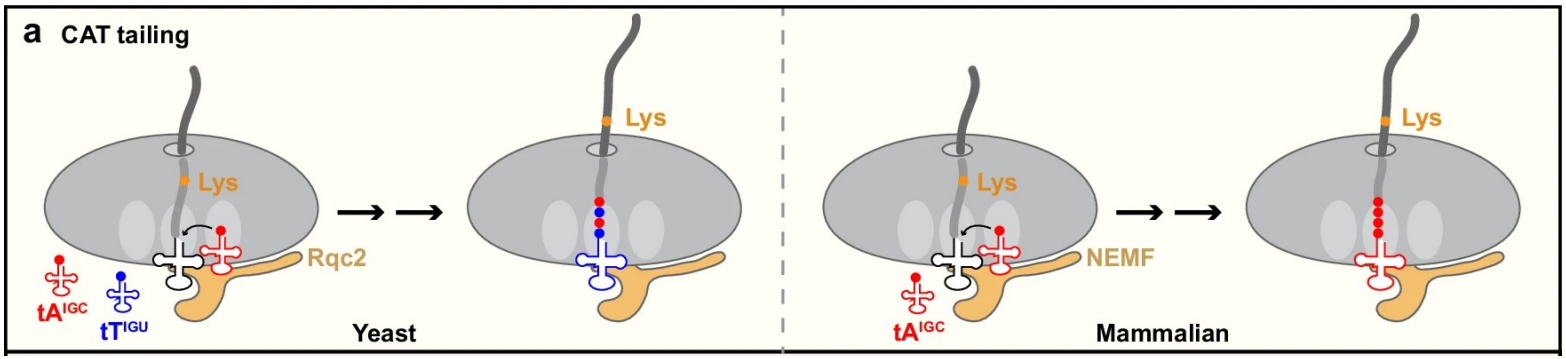


CAT tailing

Although the positioning of the Ltn1 RING domain near the ribosomal exit tunnel is well suited for ubiquitylating stalled polypeptides, this activity is limited when lysine residues are not readily accessible near the tunnel. Remarkably, Rqc2/NEMF overcomes this limitation by extending stalled polypeptides that remain anchored to the 60S subunit.

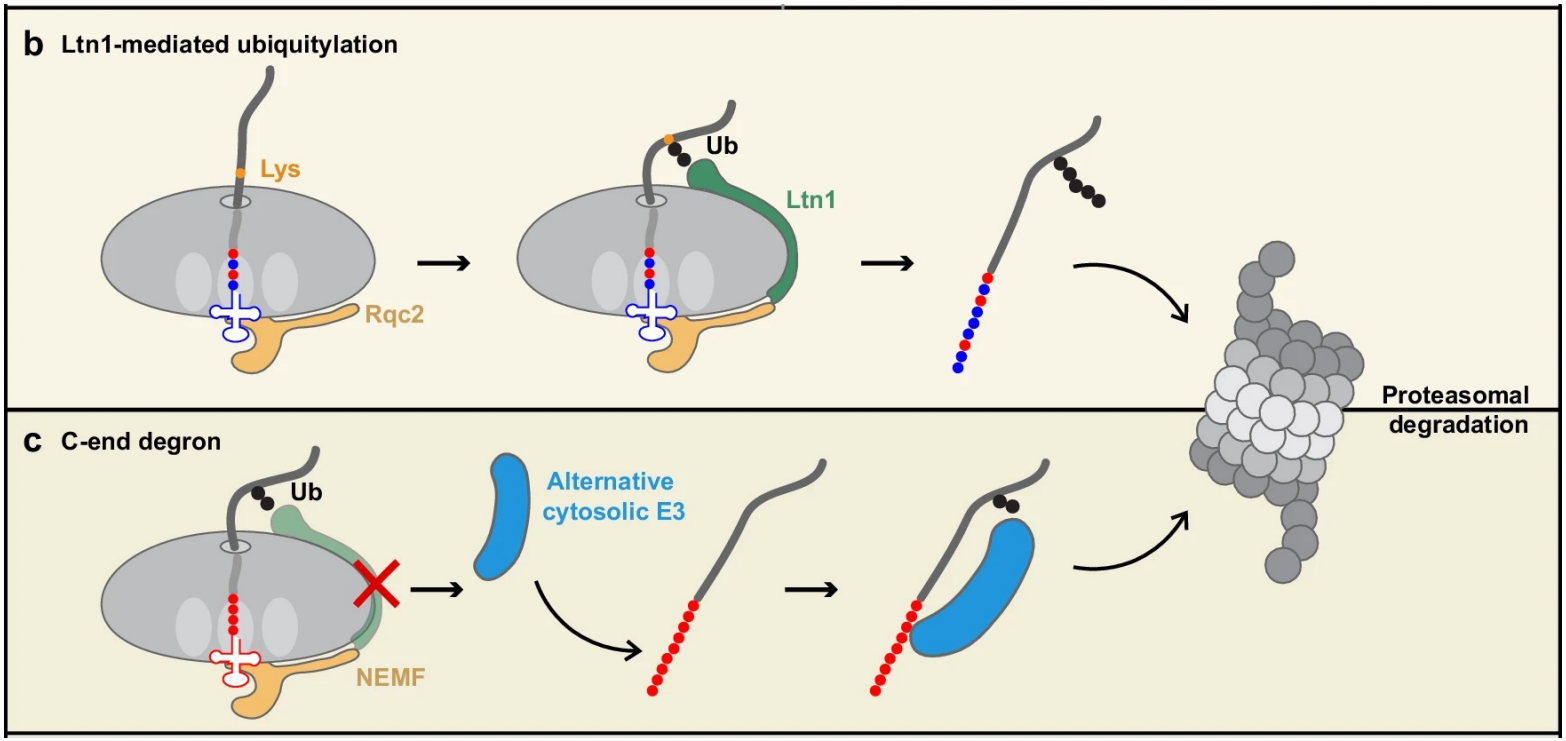
Yeast Rqc2 and human NEMF extend the C-termini of stalled polypeptides on RQC-targeted 60S subunits without requiring an mRNA template. In yeast, Rqc2 specifically recruits $tRNA^{Ala(IGC)}$ and $tRNA^{Thr(IGU)}$, generating C-terminal Ala/Thr (CAT) tails. In humans, CAT tails consist predominantly of alanine. CAT tail elongation can expose previously buried lysine residues.

Unlike canonical translation by 80S ribosomes, CAT tailing on the 60S subunit proceeds independently of GTP, suggesting that translational GTPases are not involved140. However, the process requires eIF5A, which binds to the E-site of the 60S subunit and facilitates peptidyl transfer.



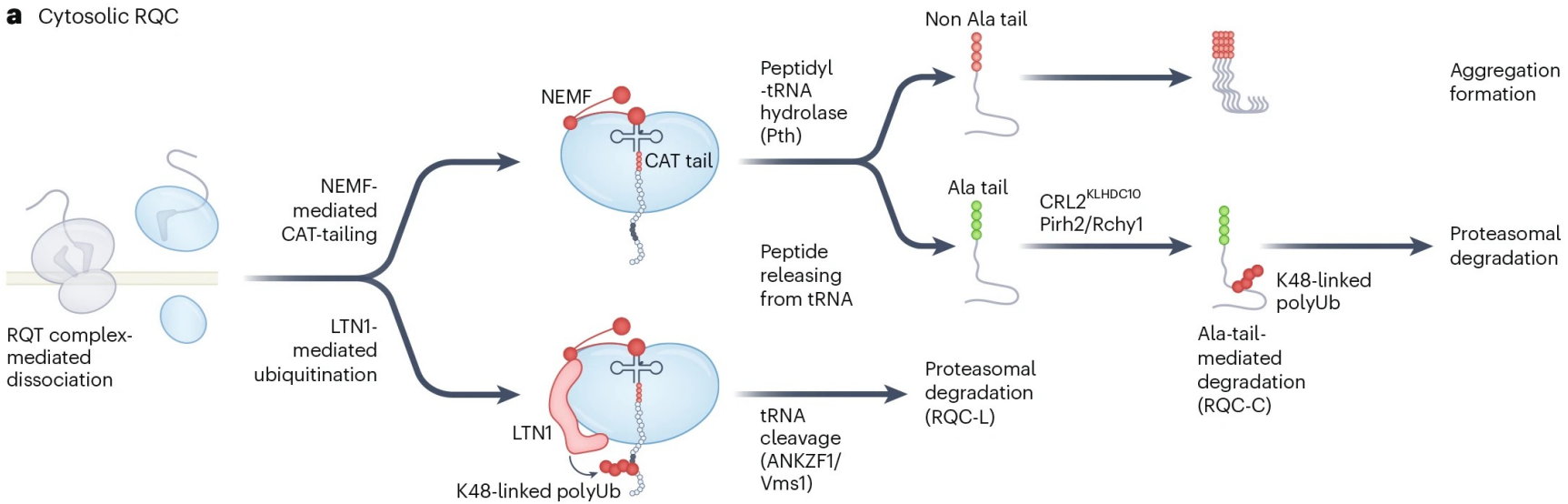
CAT tailing

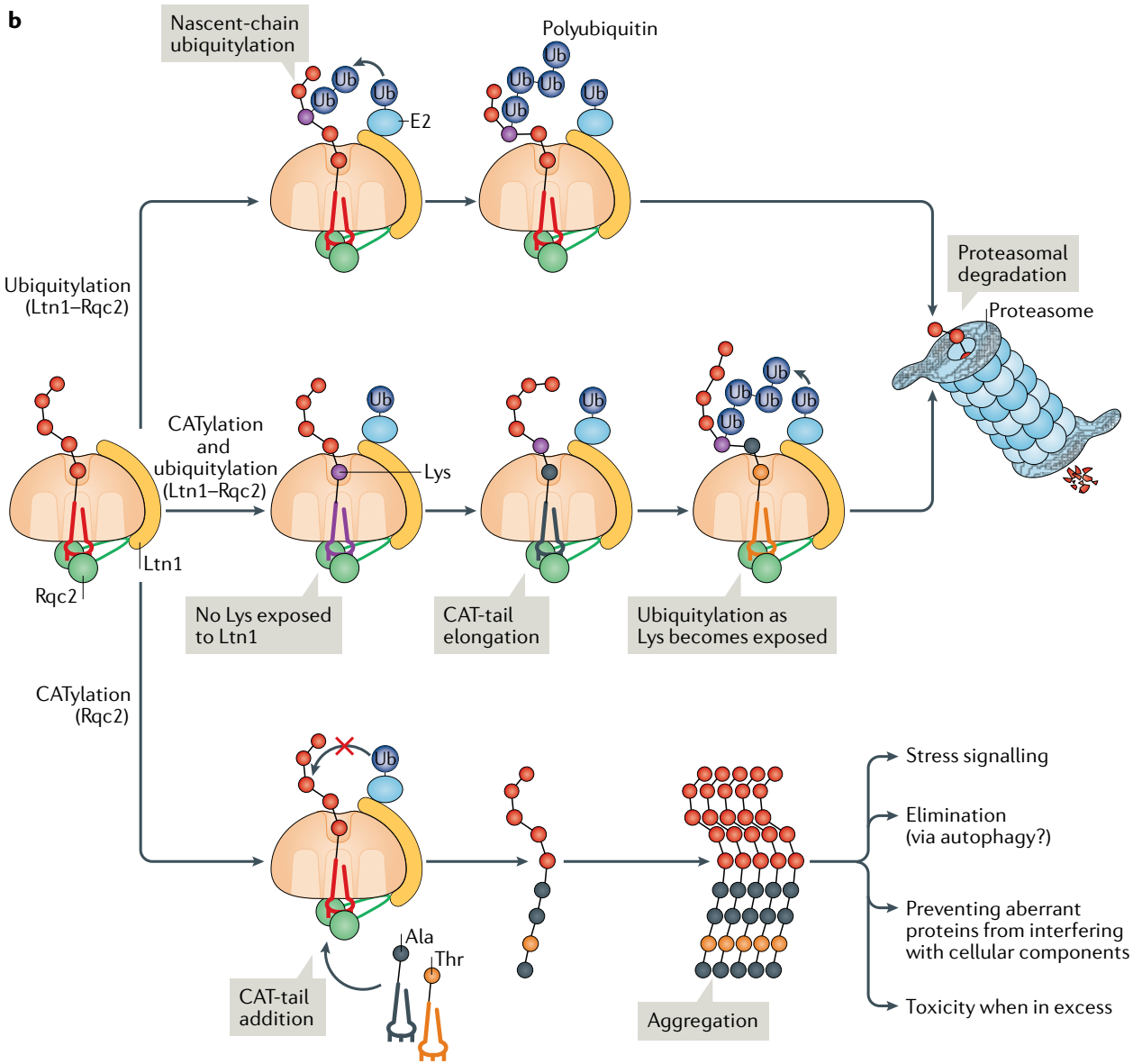
Ltn1 ubiquitylates lysine residues located near the ribosome exit tunnel. Although CAT tails enhance Ltn1-mediated ubiquitylation, they also serve as degradation signals. If stalled polypeptides escape Ltn1-mediated ubiquitylation, their CAT tails can be recognized by alternative off-ribosome E3 ligases.



Nascent-chain release

Nascent chain release can be mediated by ANKZF1 (Vms1 in yeast), which cleaves the tRNA, leaving the 3′-CCA end of tRNA attached to the peptide. This pathway may follow LTN1-mediated ubiquitination and produce tRNA fragments subject to repair or degradation. Without LTN1, release is instead carried out by Ptrh1, a peptidyl-tRNA hydrolase homolog, which hydrolyzes the ester bond, freeing peptides for proteasomal degradation. In yeast, undegraded CAT-tailed proteins form detergent-insoluble aggregates, driven by threonine residues.

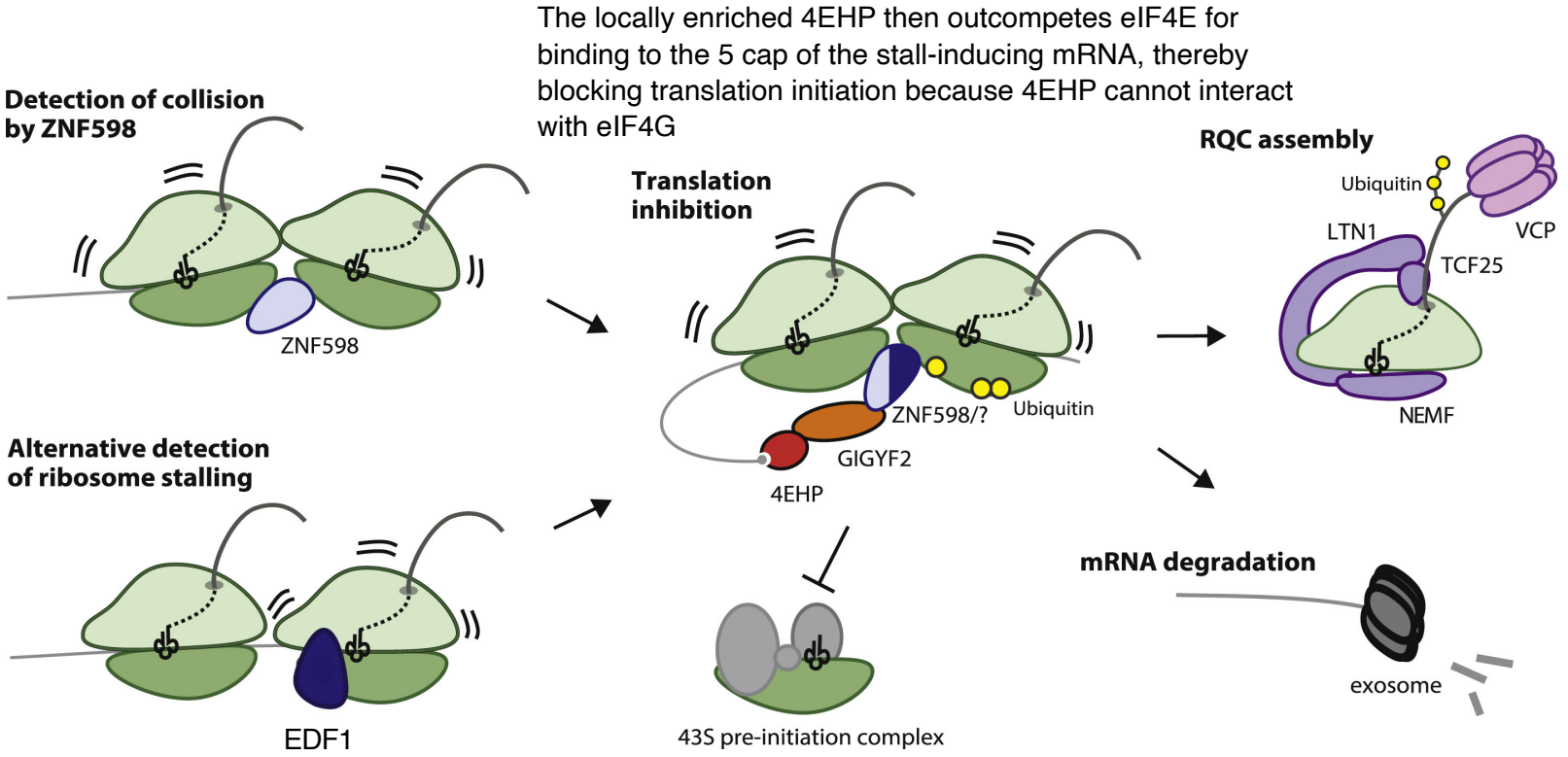




The canonical RQC pathway of Ltn1-mediated ubiquitylation of nascent polypeptides is kinetically preferred, provided that lysine ubiquitylation sites on nascent chains are readily accessible (top). In this pathway , Rqc2 functions in recruiting and stabilizing Ltn1 in the complex. An alternative pathway takes place when ubiquitylation is compromised (middle). In this pathway , Rqc2 catalyses the elongation of a CAT tail, which can result in the exposure of lysine residues that would otherwise be hidden in the ribosomal exit tunnel. The increased accessibility to lysine residues enables ubiquitylation by Ltn1. However, when ubiquitylation fails altogether (bottom), CAT-tail-modified nascent chains form aggregates, which can have different fates and effects in cellular function, including stress signalling. Ub, ubiquitin.

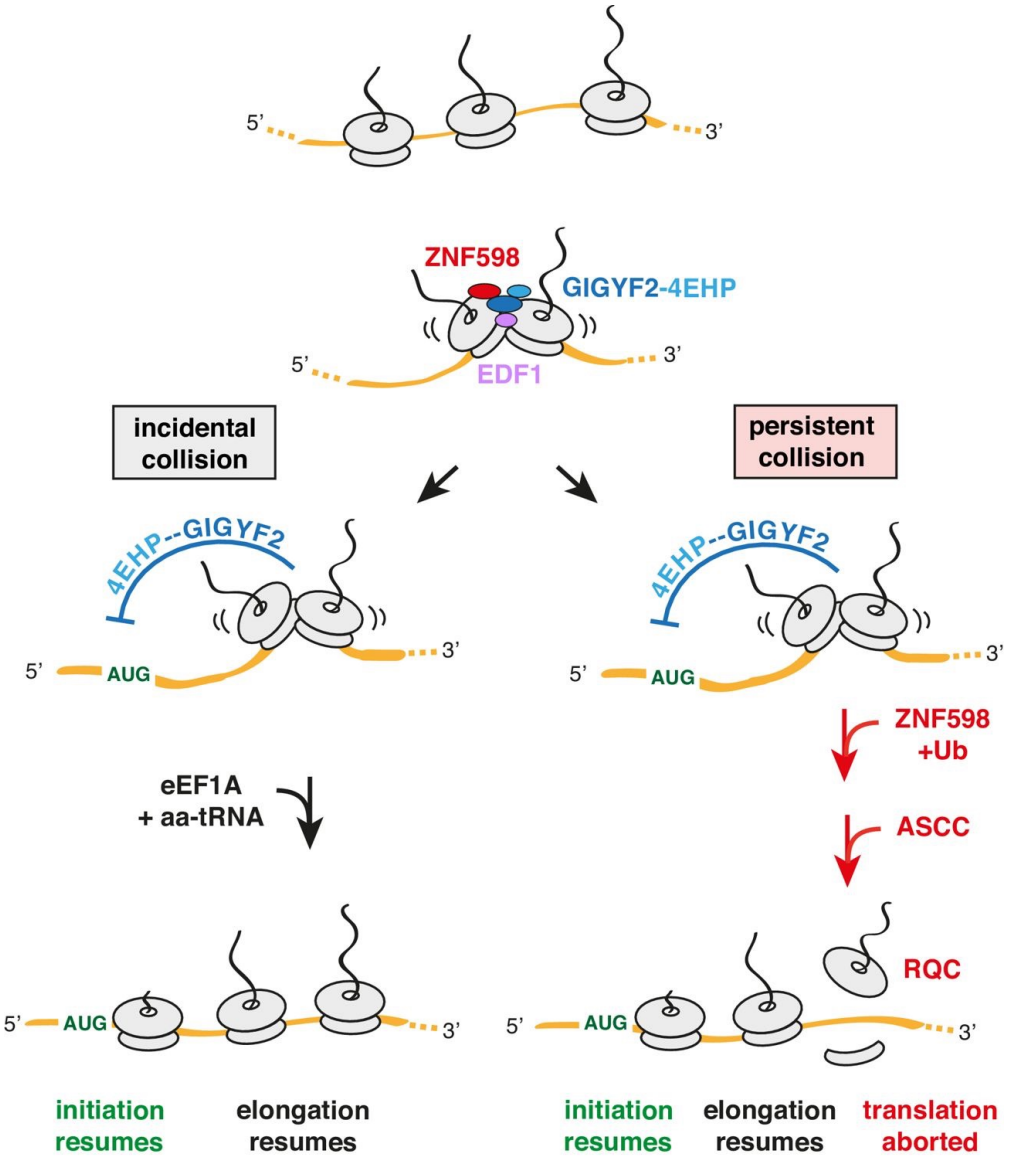
Cellular mechanisms to minimize ribosome stalling

Ribosome collision is detected by the collision sensor ZNF598. Its binding triggers a cascade of events that ultimately leads to release of the stalled ribosome and degradation of the faulty mRNA and stalled nascent peptide. In addition, ZNF598 recruits the translation inhibitors GIGYF2 and 4EHP to the defective message, which blocks further ribosome initiation. Recruitment of GIGYF2 and 4EHP to defective messages could be mediated by factors other than ZNF598, such as EDF1.

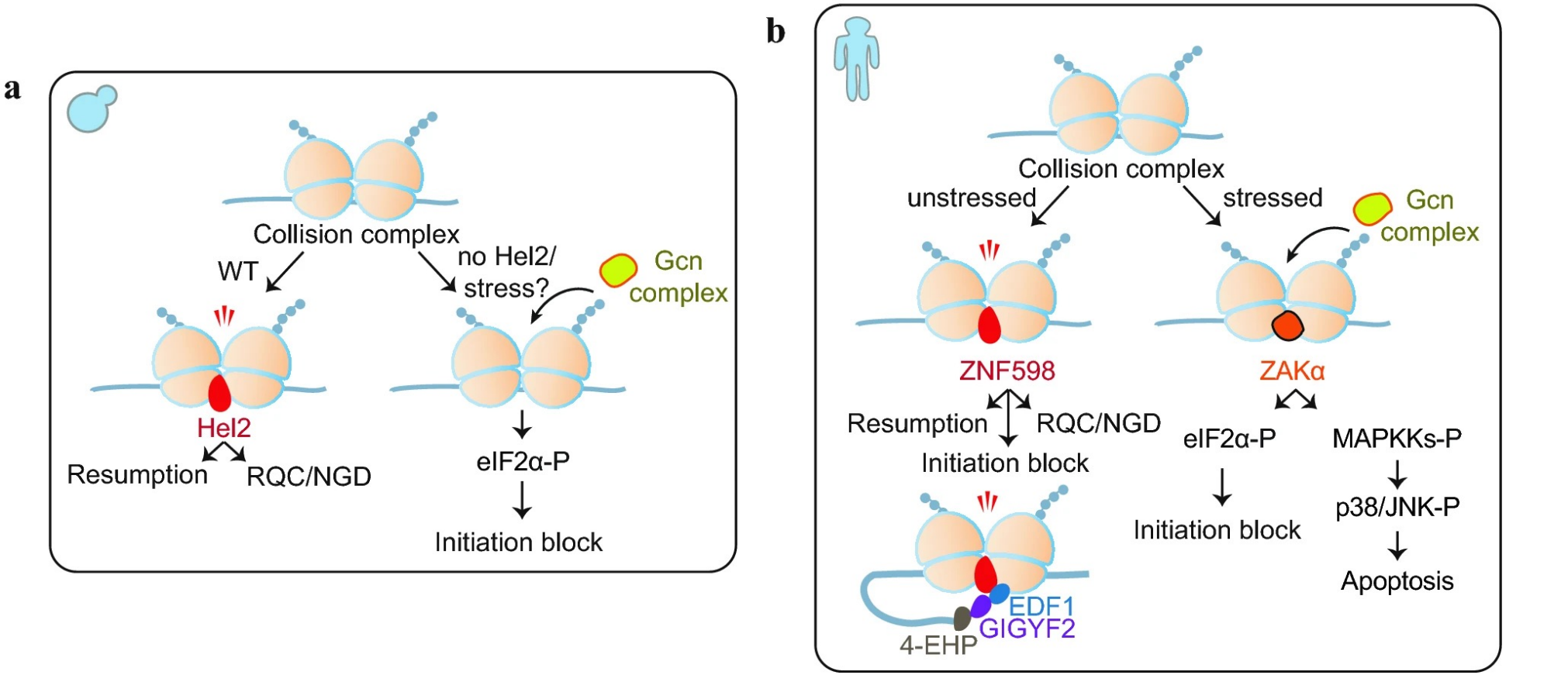


Cellular mechanisms to minimize ribosome stalling

In human cells, EDF1 functions as a collision sensor that acts independently of ZNF598, recruiting the translational repressors GIGYF2 and 4EHP to collided ribosomes. Because EDF1 is far more abundant than ZNF598, it may function as an upstream collision sensor. However, ZNF598 activity does not depend on EDF1.



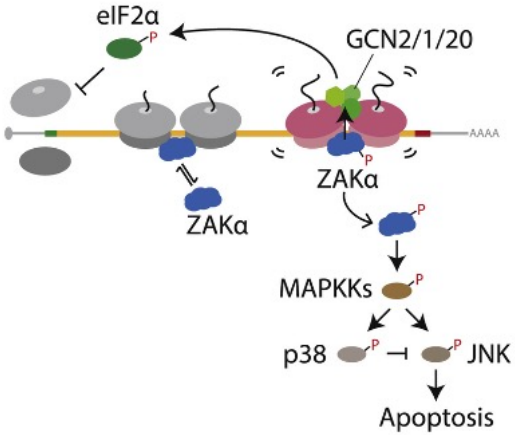
Multiple surveillance pathways recognize ribosome collisions

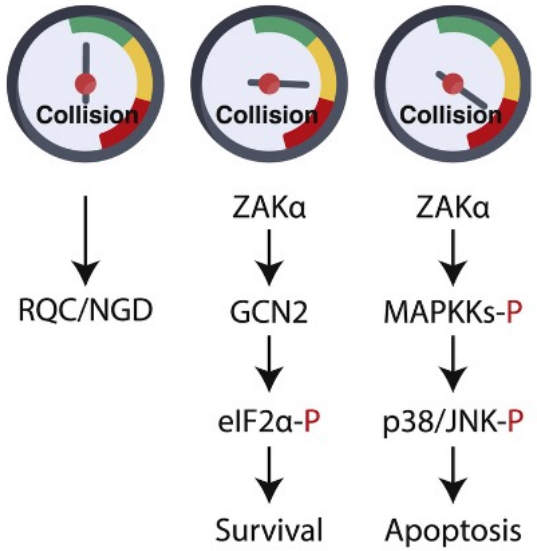


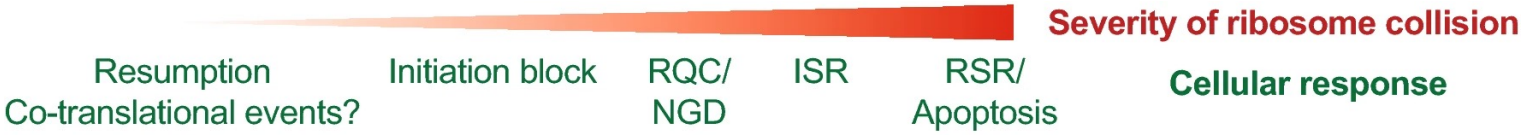
Cellular sensing of ribosome collisions can also activate stress response pathways. These include the intergrated stress response (ISR) and the ribotoxic stress response (RSR)

Multiple surveillance pathways recognize ribosome collisions

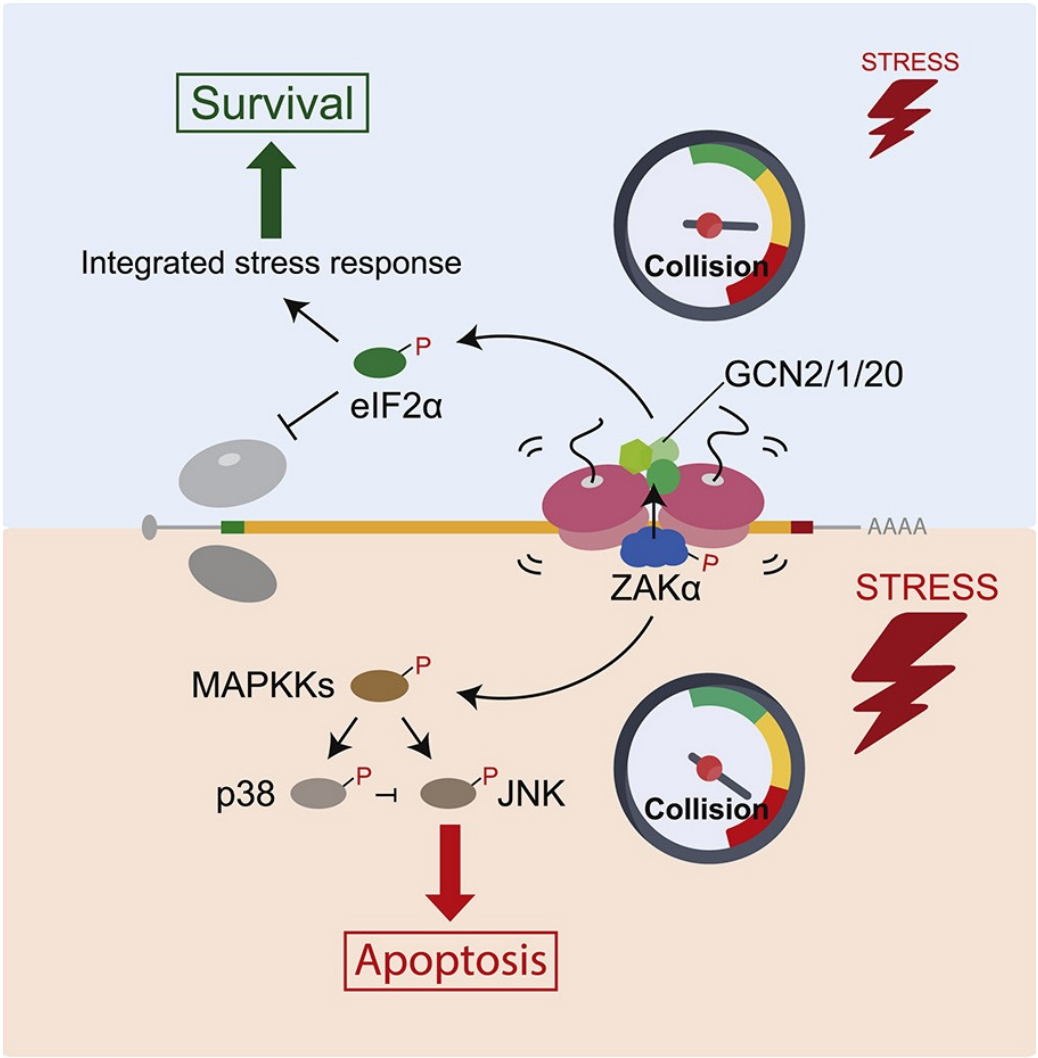
ZAK associates normally with elongating, transiently colliding, ribosomes, but under broad cellular stress, auto-phosphorylates on abundant more stable colliding ribosomes and activates downstream activation of both SAPK (p38/JNK) and GCN2 signaling pathways.







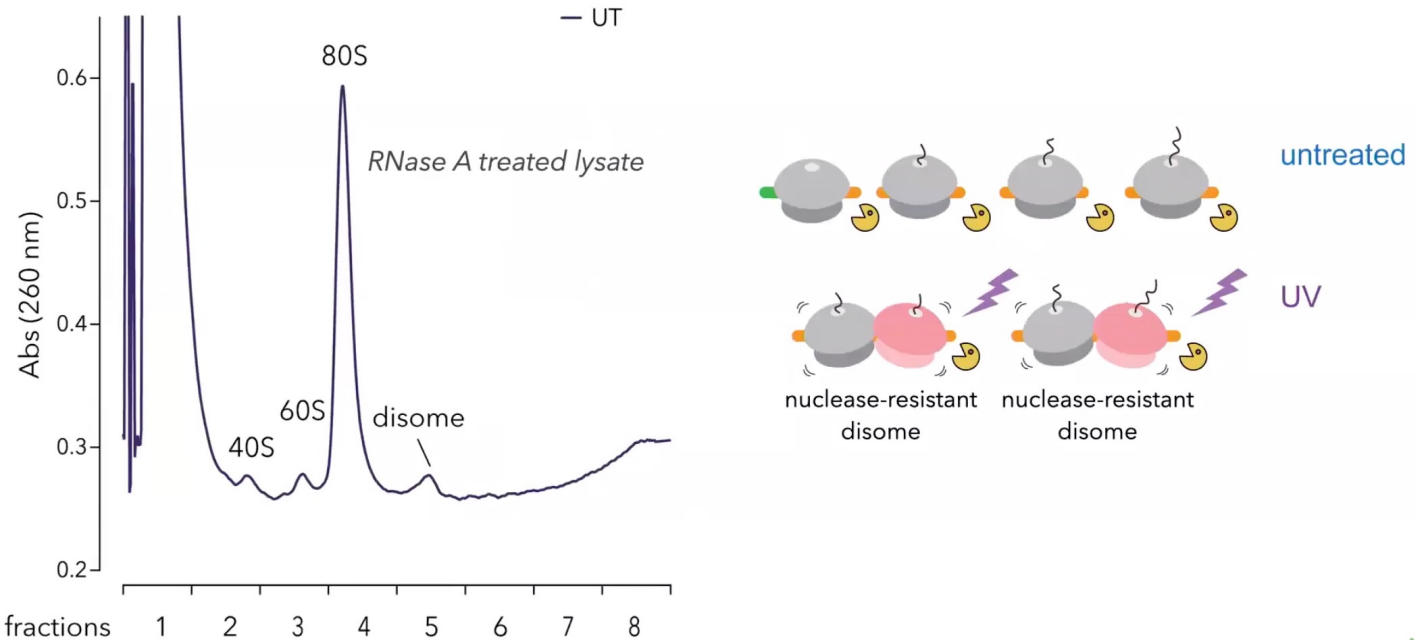
Ribosome Collisions Trigger General Stress Responses to Regulate Cell Fate

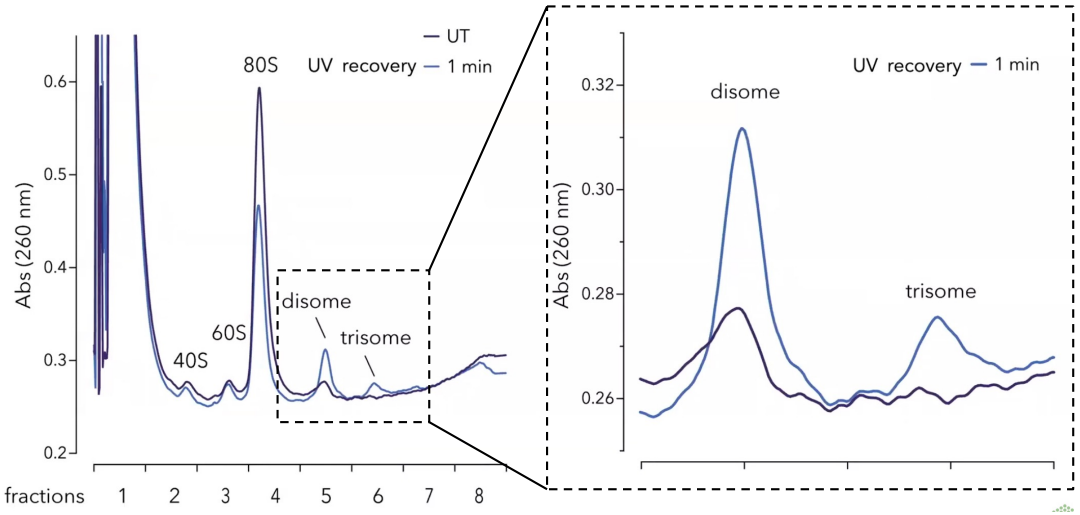


Cellular stress, such as amino acid starvation and UV irradiation, causes widespread ribosome collisions. Colliding ribosomes serve as a platform that recruits ZAKα and triggers two inter-related but distinct signaling pathways— the ribotoxic stress response and the integrated stress response—to regulate cell fate decisions.

Ribosome collision detection

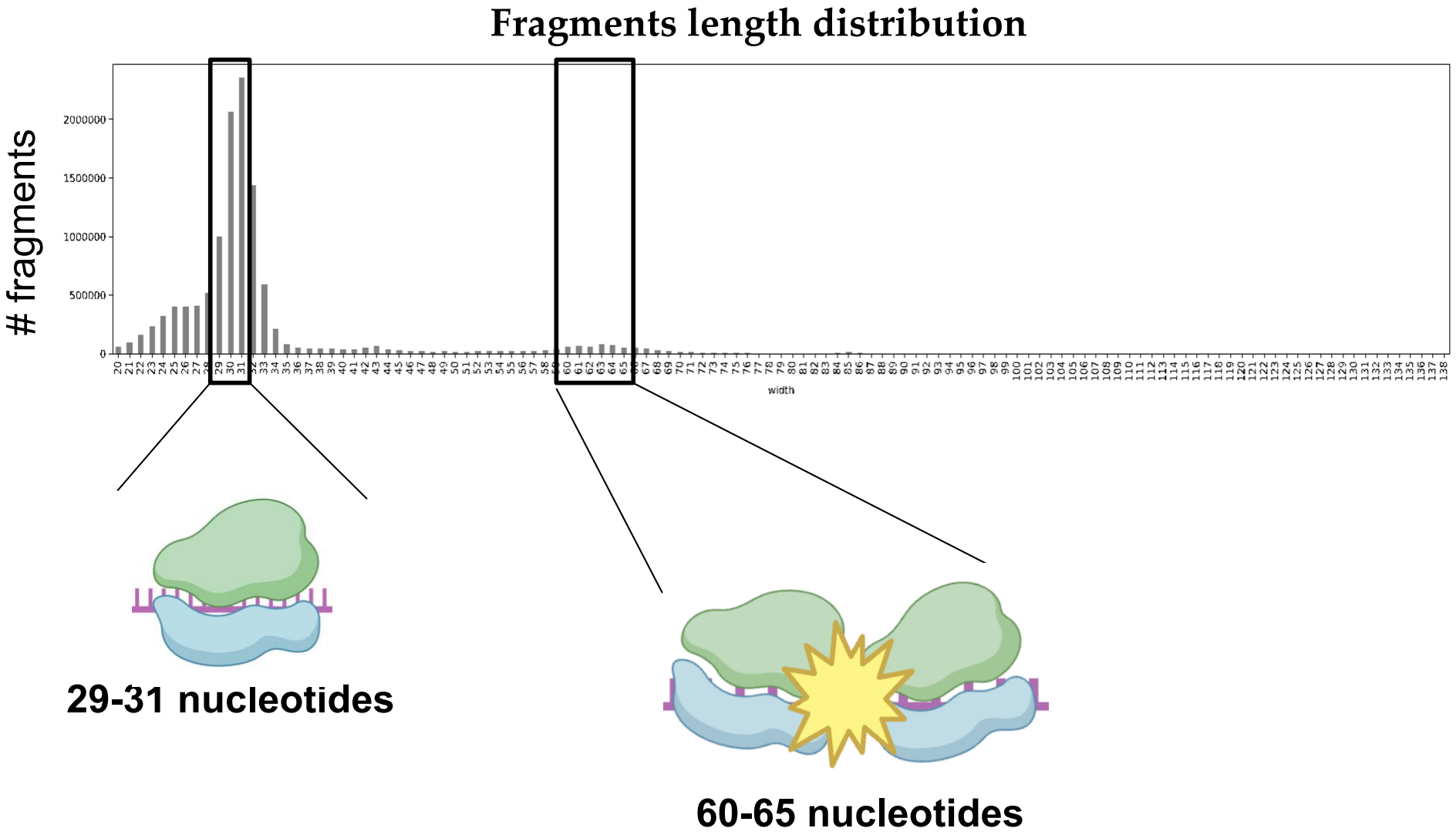
Polysomes profile





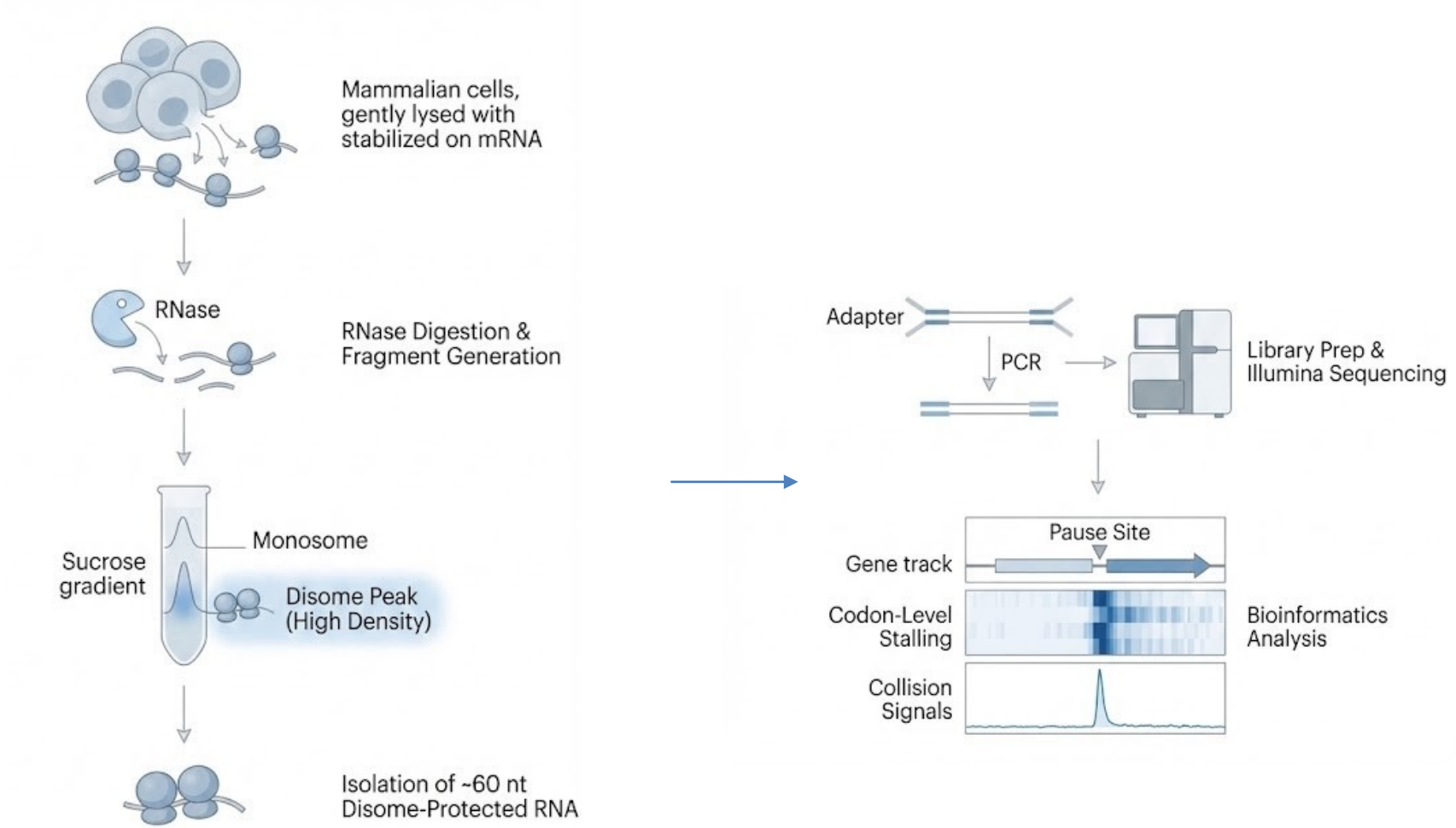
Ribosome collision detection

Polysomes profile



Disome-Seq

Disome-seq (Disome Profiling): A variation of Ribo-seq that specifically isolates mRNA fragments protected by two colliding ribosomes ("disomes") to map collision sites transcriptome-wide.



Methodologies in translational analysis

Feature	Polysome Profiling	Ribo-seq (Standard)	Disome-seq (Advanced)
Core Technology	Sucrose Gradient + UV	RNase Digestion + NGS	Disome Enrichment + NGS
Resolution	Global / Component Level	Codon (Single Ribosome)	Codon (Colliding Pair)
Primary Output	Translation Efficiency (TE)	ORF Localization	Pause Sites & Stress
Fragment Size	N/A (Full RNA)	~28-32 nt	~50-65 nt
Solves For...	"Is translation active?"	"Where is the ribosome?"	"Where is it stuck?"

Translation drives mRNA quality control

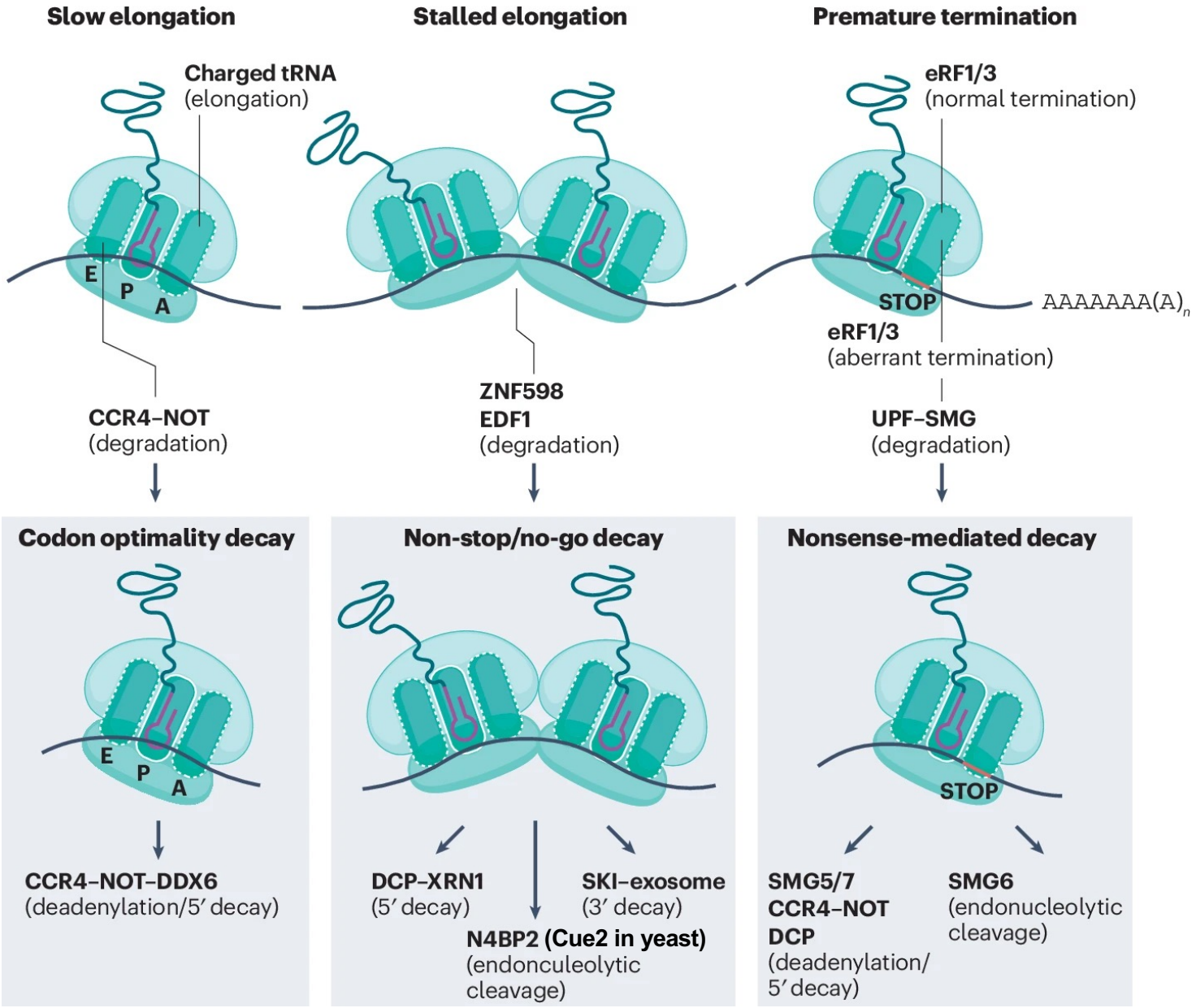
There are three predominant forms of co-translational mRNA surveillance:

1. **Codon optimality decay**, Not5 interacts with the E-site of ribosomes in which both the A- and E-sites are empty recruiting the Ccr4-Not complex;

2. **No-go decay (NGD) and nonstop decay (NSD)**, targets mRNAs stalled in translation or lacking a termination codon;

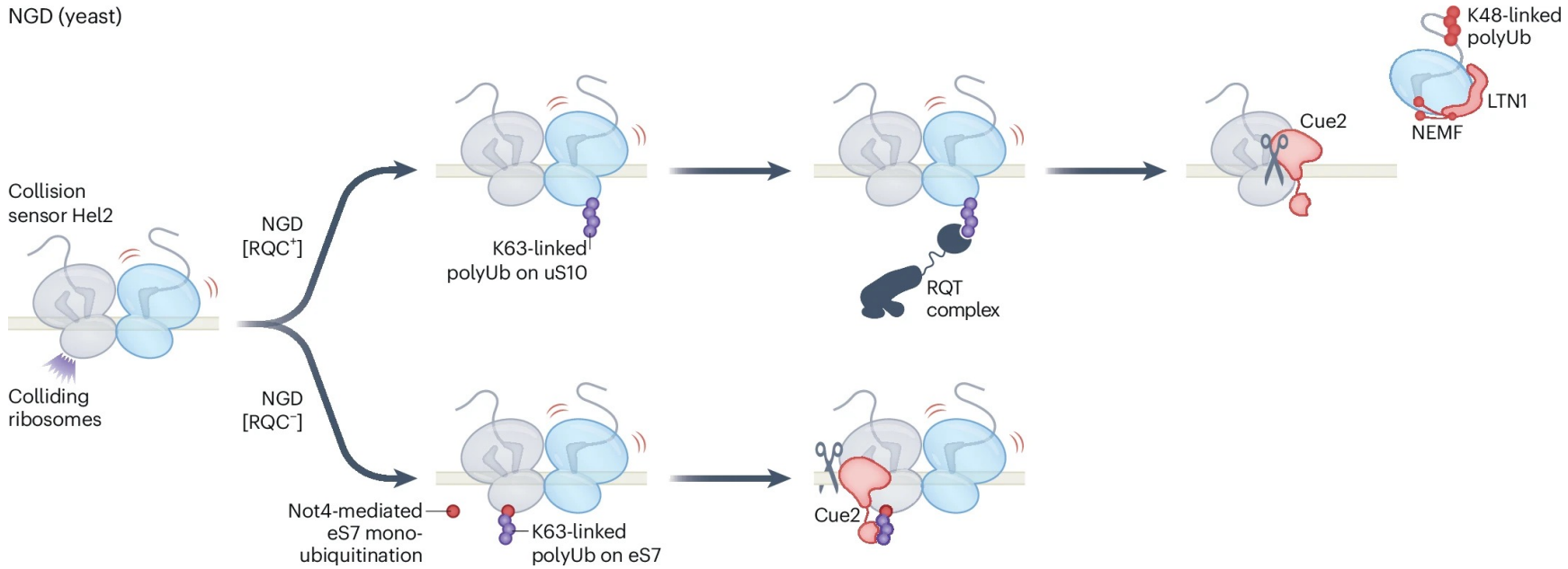
3. **Nonsense-mediated decay (NMD)**, specifically targets mRNAs containing a premature termination codon (PTC);

mRNA decay pathways that monitor the translation process



Coupling mRNA cleavage to ribosome rescue

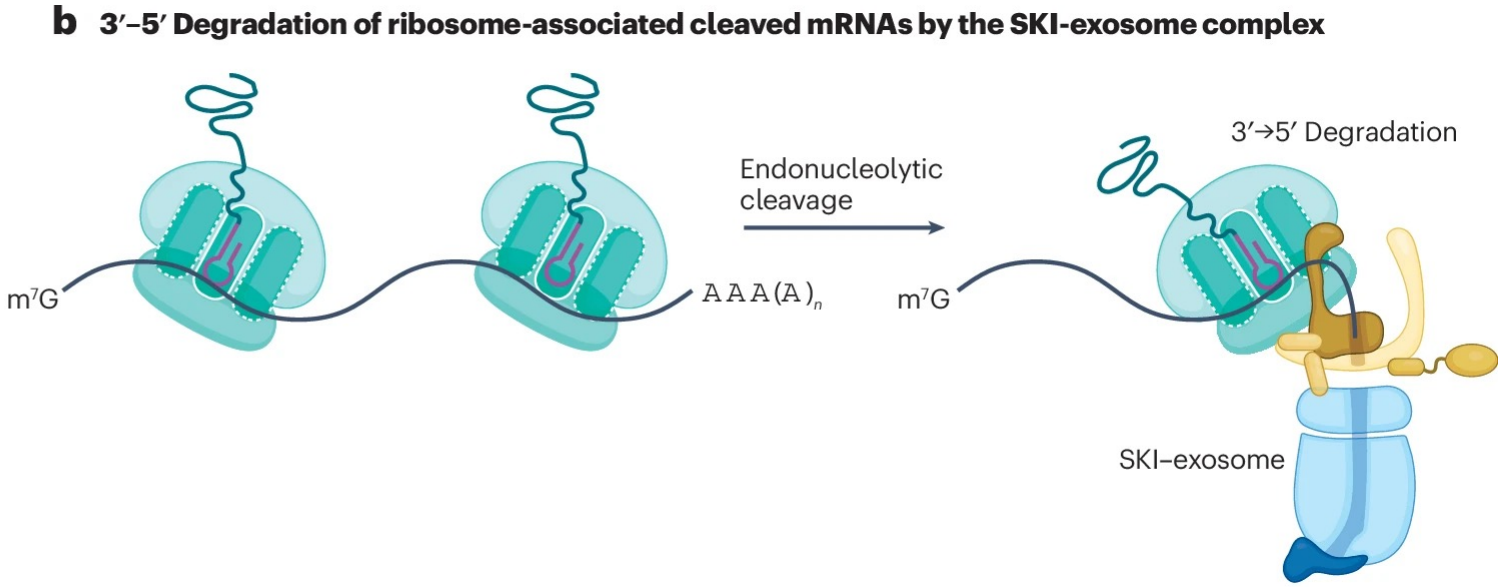
In yeast, Hel2-dependent ubiquitination of uS10 and eS7 is essential for RQC and No-Stop and No-GO decay. Cue2 acts as the endonuclease that senses persistent ribosome collisions by recognizing ubiquitinated ribosomes and cleaving mRNA at defined sites. NGD follows two routes: a Slh1-dependent branch coupled to RQT-mediated subunit splitting, in which Cue2 cleaves near the collided ribosome, and an Slh1-independent branch, in which Not4-mediated mono-ubiquitination and Hel2-mediated K63 polyubiquitination of eS7 recruit Cue2 to cut just upstream of the disome. Although the exact cleavage-site rules remain unclear, Hel2-driven ubiquitin signals direct Cue2-mediated mRNA cleavage to link ribosome rescue with targeted decay. In mammals, whether collisions induce similar endonucleolytic cleavage remains unresolved.



Coupling mRNA cleavage to ribosome rescue

A primary function of the cytoplasmic SKI–exosome complex lies in the degradation of translating mRNAs that have undergone internal cleavage that causes, or results from, an aberrant translation event.

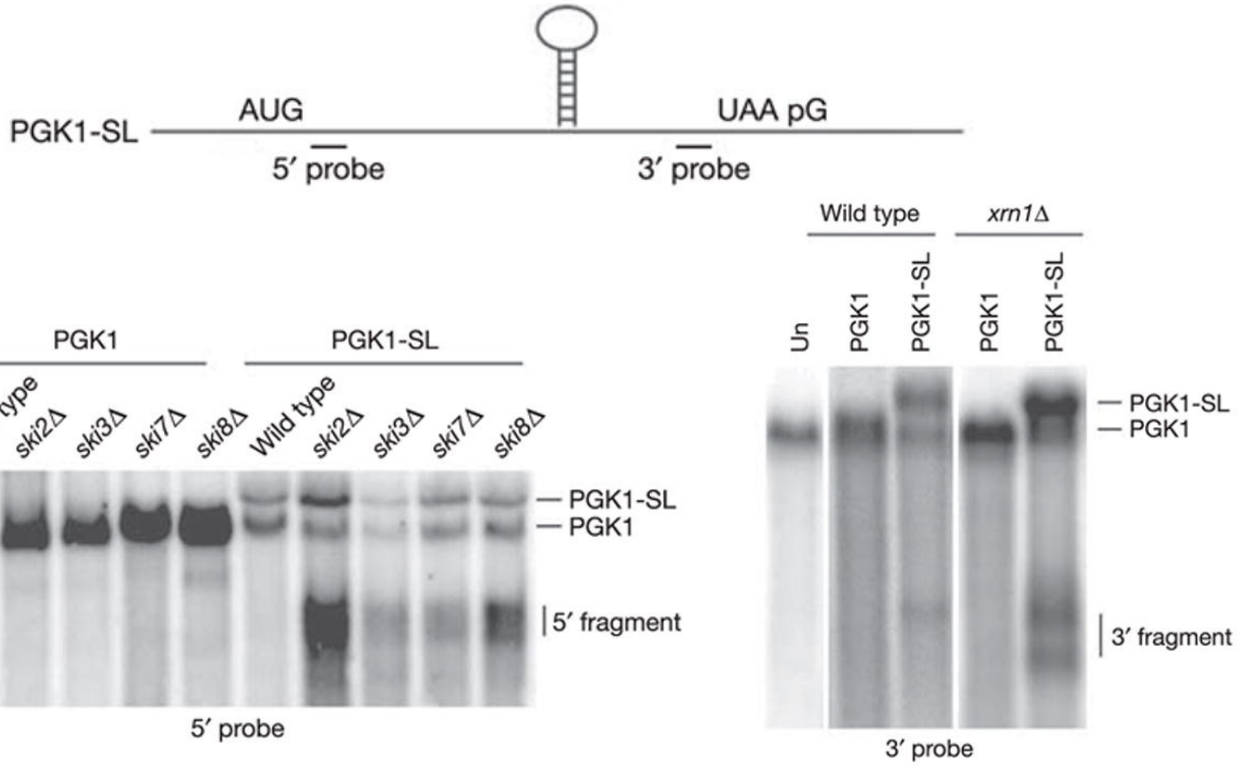
Structural studies have demonstrated a direct interaction of the SKI complex with the ribosome near the mRNA entry tunnel, and biochemical studies have demonstrated the ability of the SKI complex to extract RNA from stalled ribosomes



No-GO mRNA decay (NGD)

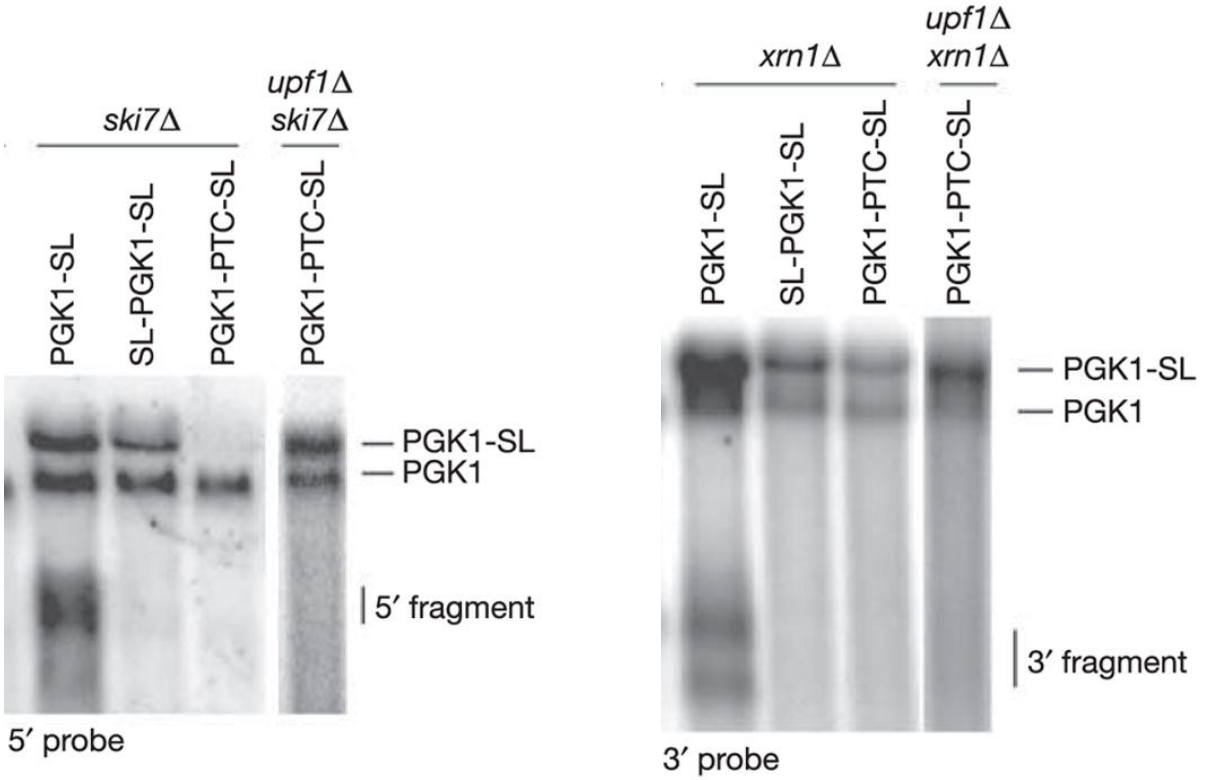
•**NGD** involves endonucleolytic cleavage(s) near to where the translationally active ribosome stalls.

•It was discovered when an artificial stem–loop structure was inserted into mRNAs, creating a block to translation elongation. Stalling of elongating ribosomes leads to endonucleolytic cleavage of the PGK1-SL reporter transcript

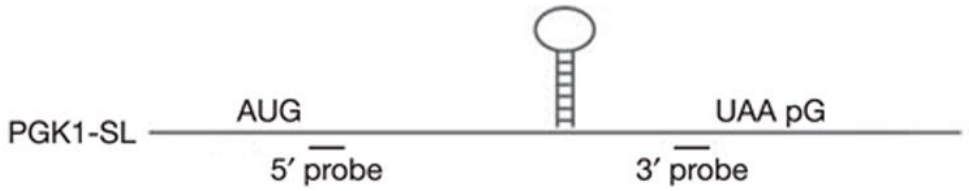


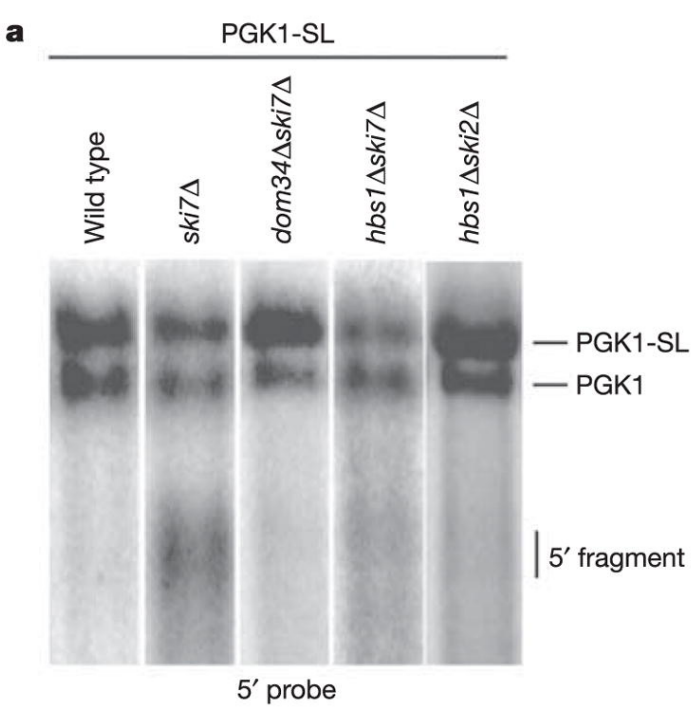
NGD is dependent on translation by ribosomes

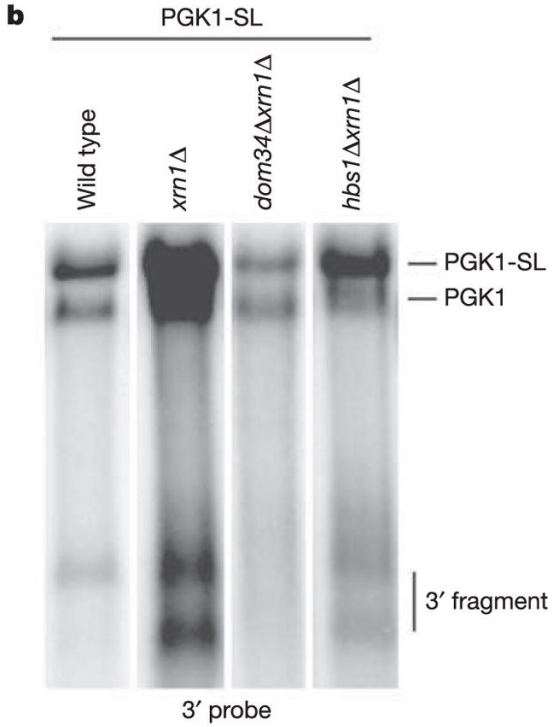
- block of translation initiation (stem loop in the 5’-UTR) or PTC (Premature termination codon) prevents the accumulation of the 5′ and 3′ decay intermediates in the *ski7Δ and xrn1Δ strains*



Dom34p and Hbs1p affect NGD

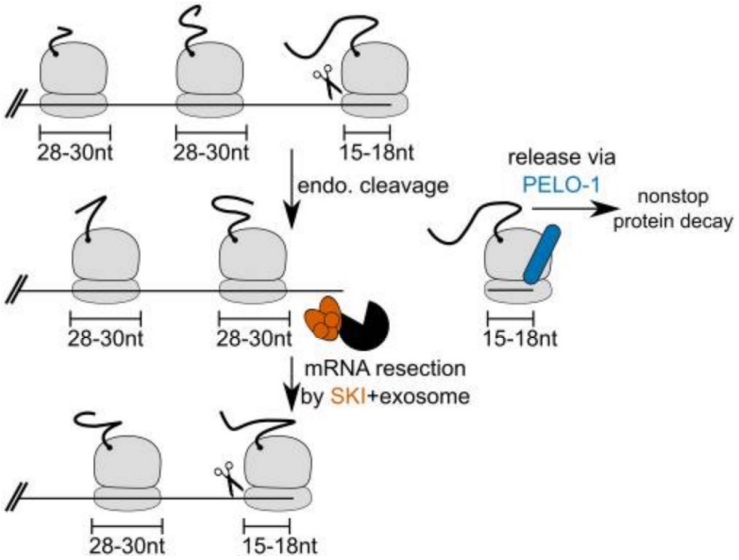


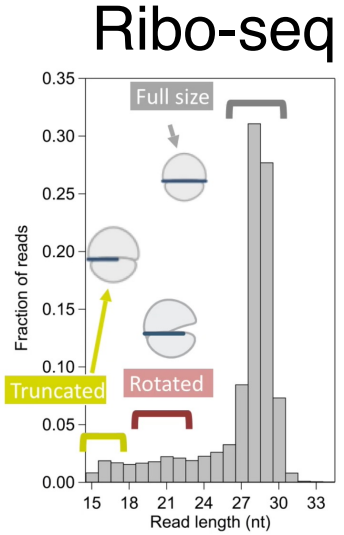


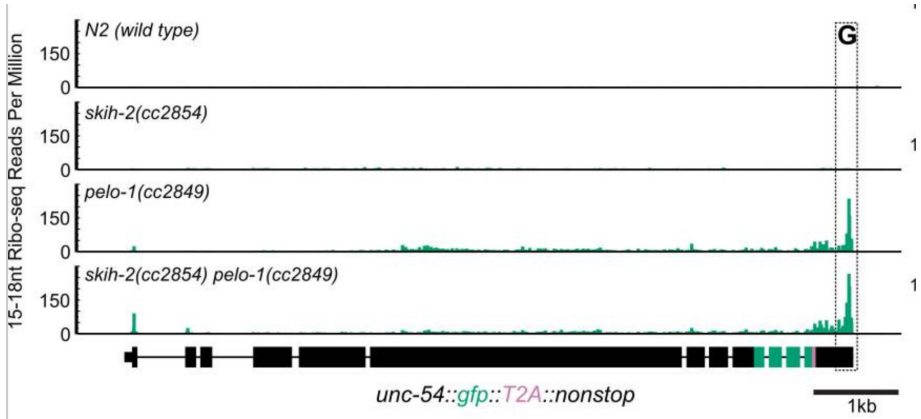


Nonstop mRNA decay (NSD)

In NSD ribosomes elongate to the end of an mRNA with no stop codons. This triggers endonucleolytic cleavage at the 5′-edge of the ribosome. The resulting 3′-end is a substrate for SKI complex and the 3′>5′ exosome, while the downstream ribosome is subjected to PELO-1-dependent rescue and nonstop protein decay.







Coupling mRNA cleavage and ribosome rescue

In conditions in which upstream rescue of ribosome collision by RQC is compromised, the Cue2 pathway becomes a primary route, highlighting its role as a fail-safe sensor that converts a persistent collision into an irreversible clearance event. Conversely, it is conceivable that ribosomes stalled at an mRNA 3′ end if not rescued by Pelota/Dom34 will eventually collide and be targeted by the ZNF598/Hel2 pathway.

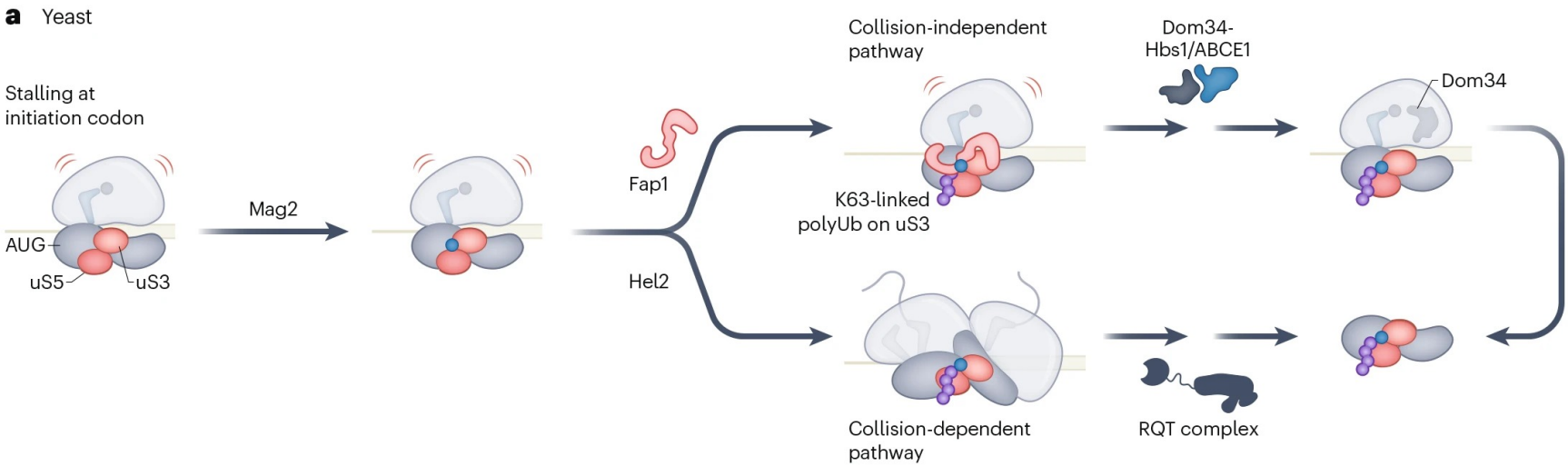
Non-functional 18S-rRNA decay (NRD)

18S nonfunctional rRNA decay (18S NRD) is a translation-coupled surveillance pathway that eliminates small-subunit rRNAs when their decoding function is compromised due to mutations or processing errors.

After rescue, the defective 18S rRNA is primarily degraded by cytoplasmic nucleases, including Xrn1 and the exosome, often in association with P bodies. Therefore, 18S NRD is both mechanistically and spatially linked to translation-dependent mRNA quality control.

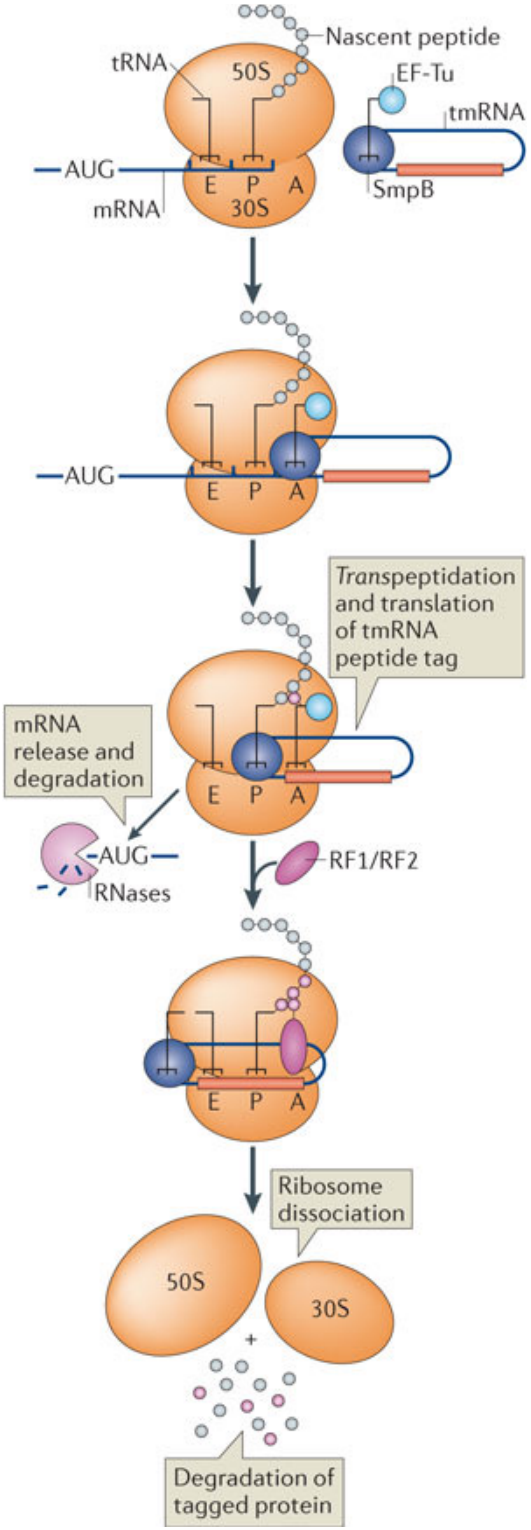
Non-functional 18S-rRNA decay (NRD)

Mag2 recognizes a slow-translating ribosome and monoubiquitinates uS3. Then, Fap1 recognizes paused monosomes and initiates 18S NRD by promoting K63-linked polyubiquitination of uS3. Cryo-EM structures of Fap1-bound ribosomes show Fap1 contacting mRNA at both the entry and exit channels, enabling detection of mRNA stasis and sterically preventing formation of collided disomes. Dom34-Hbs1 is involved in the dissociation of the stalled ribosome. Bottom (collision-dependent pathway): cells commonly detect problematic translation by sensing collided ribosomes and activating RQC and 18S NRD. Hel2 recognizes collided disomes containing a stalled ribosome with monoubiquitinated uS3 and extends K63-linked polyubiquitin on uS3. The RQT complex binds this chain, splits the stalled ribosome and promotes degradation of the 40S subunit. The coupling of RQC and 18S NRD remains unclear



Lesson from bacteria

In bacteria, mRNAs that lack an in-frame stop codon (non-stop mRNA) and the associated nascent protein are degraded by the ***trans*-translation mechanism**. *Trans*-translation relies on two main factors: **small stable 10S RNA (ssrA)**, an aminoacylated transfer-messenger RNA (tmRNA) with properties both of a tRNA and an mRNA; and **SmpB**. The trimeric complex **SmpB–tmRNA–EF-Tu** binds to the A-site of stalled ribosomes. The tmRNA tRNA domain is located close to the ribosome peptidyl transferase centre, and SmpB contacts the mRNA. The nascent polypeptide is transferred from the P-site tRNA to the A-site tmRNA. The non-stop mRNA is consequently released and rapidly degraded by RNAses. Next, the mRNA moiety of tmRNA drives the synthesis of a **peptide tag** linked to the carboxyl terminus of the truncated nascent peptide. This tag triggers the rapid degradation of the protein fusion by cellular proteases



nature

Article

Synthetic lethality of mRNA quality control complexes in cancer

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Check for updates

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Synthetic lethality exploits the genetic vulnerabilities of cancer cells to enable a targeted, precision approach to treat cancer[1]. Over the past 15 years, synthetic lethal cancer target discovery approaches have led to clinical successes of PARP inhibitors[2] and ushered several next-generation therapeutic targets such as WRN[3], USP1[4], PKMYT1[5], POLQ[6] and PRMT5[7] into the clinic. Here we identify, in human cancer, a novel synthetic lethal interaction between the PELO–HBS1L and SKI complexes of the mRNA quality control pathway. In distinct genetic contexts, including 9p21.3-deleted and high microsatellite instability (MSI-H) tumours, we found that phenotypically destabilized SKI complex leads to dependence on the PELO–HBS1L ribosomal rescue complex. PELO–HBS1L and SKI complex synthetic lethality alters the normal cell cycle and drives the unfolded protein response through the activation of IRE1, as well as robust tumour growth inhibition. Our results indicate that PELO and HBS1L represent novel therapeutic targets whose dependence converges upon SKI complex destabilization, a common phenotypic biomarker in diverse genetic contexts representing a significant population of patients with cancer.

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Article

SKI complex loss renders 9p21.3-deleted or MSI-H cancers dependent on PELO

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Cancer genome alterations often lead to vulnerabilities that can be used to selectively target cancer cells. Various inhibitors of such synthetic lethal targets have been approved by the FDA or are in clinical trials, highlighting the potential of this approach[1–3]. Here we analysed large-scale CRISPR knockout screening data from the Cancer Dependency Map and identified a new synthetic lethal target, *PELO*, for two independent molecular subtypes of cancer: biallelic deletion of chromosomal region 9p21.3 or microsatellite instability-high (MSI-H). In 9p21.3-deleted cancers, *PELO* dependency emerges from biallelic deletion of the 9p21.3 gene *FOCAD*, a stabilizer of the superkiller complex (SKIc). In MSI-H cancers, PELO is required owing to MSI-H-associated mutations in *TTC37* (also known as *SKIC3*), a critical component of the SKIc. We show that both cancer subtypes converge to destabilize the SKIc, which extracts mRNA from stalled ribosomes. In SKIc-deficient cells, PELO depletion induces the unfolded protein response, a stress response to accumulation of misfolded or unfolded nascent polypeptides. Together, our findings indicate *PELO* as a promising therapeutic target for a large patient population with cancers characterized as MSI-H with deleterious *TTC37* mutations or with biallelic 9p21.3 deletions involving *FOCAD*.

PELO loss and impairment of SKIc synergize to activate multiple stress pathways